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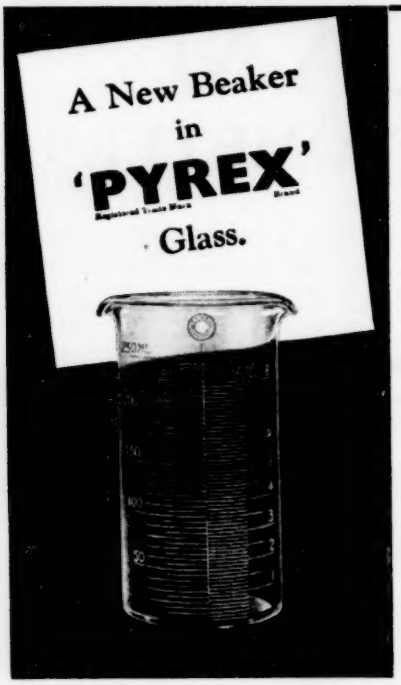

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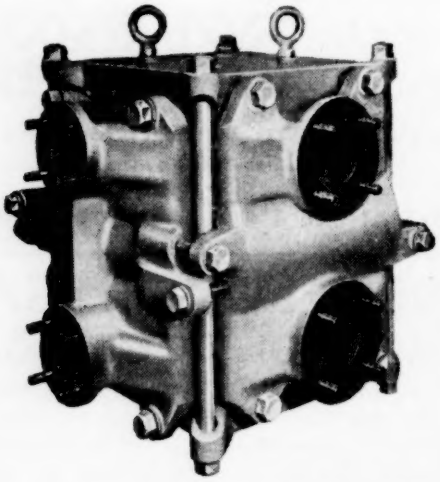

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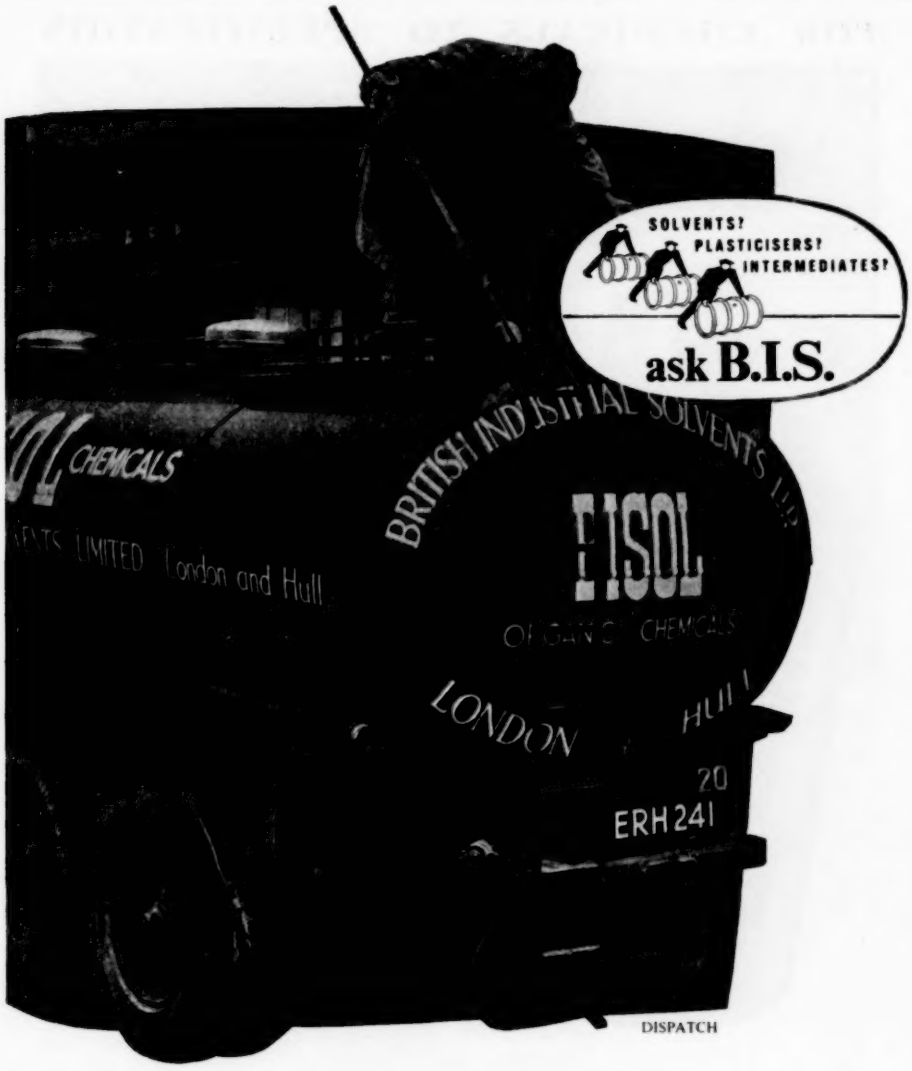

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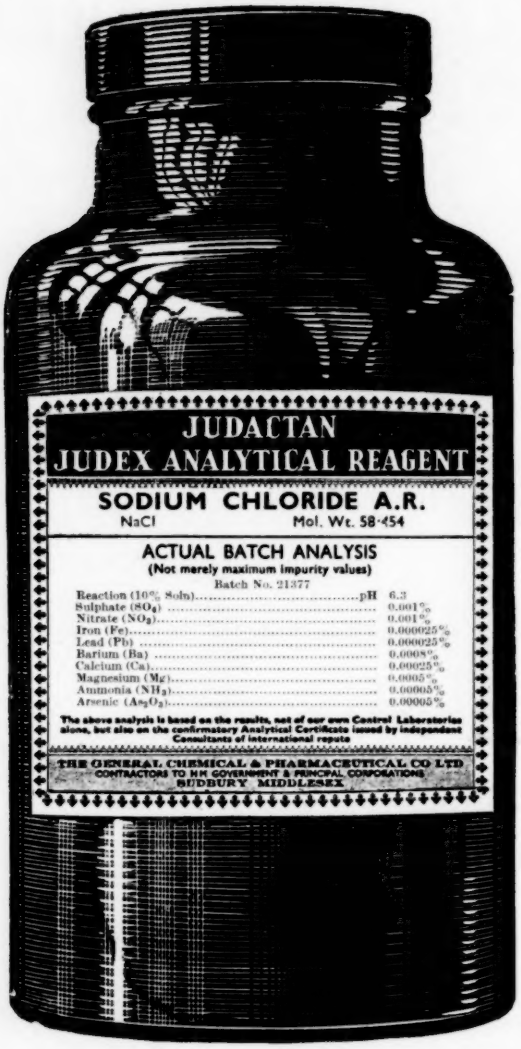
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57. *The Nature of the Co-ordinate Link. Part V.* The Equilibrium between* cis- *and* trans-*Bis(triethylphosphine)dichloroplatinum.*

By J. Chatt and R. G. Wilkins.

The isomerisation of *cis*-$(PEt_3)_2PtCl_2$ in benzene solution at 20—35° is an endothermic reaction, $\Delta H = 2470$ cal./mole, $\Delta G = -1480$ cal./mole, $\Delta S = 13{\cdot}3$ cal. mole^{-1} degree^{-1}. After allowance has been made for possibly greater association of benzene with the *cis*-isomer (to account for the entropy change) and a large liberation of energy owing to favourable spatial redistribution of electric charge when the highly polar *cis*- is converted into the non-polar *trans*-isomer, the *cis*-isomer is found to be more stable than the *trans* to the extent of about 10 000 cal. This represents the increase in bond energy when the phosphorus atoms are in *cis*- as compared with *trans*-configuration and gives strong support to the view that π-bonding through *d*-orbitals in the phosphorus and the platinum atoms plays a significant part in the binding.

In Part I of this series (*J.*, 1950, 2308) it was reported, on the basis of the crude measurements of the change in equilibrium position between *cis*- and *trans*-$(PPr^n_3)_2PtCl_2$ at 160° and 195°, that the heat content of the *trans*- is greater than that of the *cis*-isomer; nevertheless, the equilibrium mixture contained only 3·2% (at 25°) of *cis*-material, indicating a fairly large entropy difference between these two isomers. These observations are in marked contrast with the thermodynamic relation of geometric isomers in carbon chemistry, where entropy changes are almost zero and the heat content of the *cis*- is usually greater than that of the *trans*-isomer. A greater stability of the *cis*-isomer is to be expected if *d*-orbitals contribute in some special manner, probably by π-bonding, to the strength of the P–Pt bonds to a greater (or smaller) extent than to the Pt–Cl bonds (Chatt, *Nature*, 1950, **165**, 637; Chatt and Williams, *J.*, 1951, 3061). It was therefore important to make exact measurements of equilibria in this series of complexes.

Bis(triethylphosphine)dichloroplatinum was chosen for this study because the position of equilibrium is more favourable for exact measurement than in the propyl series. Also there is possible ambiguity regarding the true value of the equilibrium constant in the latter case because the equilibrium mixtures prepared from *cis*- and from *trans*-$(PPr_3)_2PtCl_2$ were not exactly identical. In the ethyl series this effect is so slight as to be negligible (see p. 277).

cis- and *trans*-$(PEt_3)_2PtCl_2$ do not isomerise spontaneously in solution at room temperature or in benzene at the boiling point, but isomerisation occurs rapidly in solution at room temperature in the presence of a trace of free triethylphosphine and spontaneously in ethyl alcohol at 100° (Cahours and Gal, *Compt. rend.*, 1870, **70**, 891). The equilibrium may be quenched by the addition of a trace of $(PEt_3)_2Pt_2Cl_4$, sufficient to react with all the free phosphine (cf. Chatt and Wilkins, *J.*, 1951, 2532). Separation of the isomers in the quenched equilibrium mixture by extraction of the *trans*- from the insoluble *cis*-isomer with ether is sufficiently accurate to give the approximate position of equilibrium. Samples of the pure *cis*- and the pure *trans*-isomer were isomerised in benzene at 25° and both isomers were separated quantitatively from the quenched equilibrium mixture, weighed, and identified by mixed melting points. Thus it was demonstrated that only these two isomers were present in the mixture; no side reactions were detectable, and the equilibrium concentrations of each isomer thus determined agreed, within the lower limits of accuracy of this method, with those found by the following less direct method.

The *cis*- has a large dipole moment (10·7 D) and the *trans*-isomer a zero moment (Jensen, *Z. anorg. Chem.*, 1936, **229**, 250). Thus we were able to determine accurately, by dielectric-constant measurement of benzene solutions, the equilibrium concentration of *cis*-isomer. The effects of the relatively large equilibrium concentration of *trans*-isomer and of the trace of triethylphosphine catalyst were both accurately allowed for.

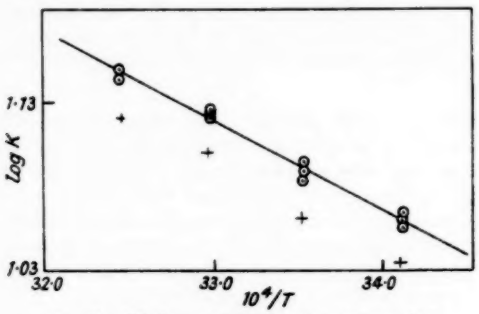
* Part IV, *J.*, 1951, 3061.

The reaction *cis*-$(PEt_3)_2PtCl_2 \rightleftharpoons$ *trans*-$(PEt_3)_2PtCl_2$ was investigated in benzene solution. Only 7·6% of *cis*- is present in equilibrium with its *trans*-isomer at 25°. The dielectric-constant method being used, the equilibrium constant (K), for this reaction was determined at different temperatures in the range 20—35° and less accurately at 45° and 60°. The relationship (see figure) :

$$\log K = 2{\cdot}901 - 540/T \quad (T = 293\text{—}308°\ \text{K})$$

was computed from these values by the method of least squares, and the following thermodynamic functions at 25° were obtained :

ΔH = heat absorbed in the reaction = 2470 ± 210 15°-cal.
ΔG = change in free energy = −1480 ± 12 cal.
ΔS = change in entropy = 13·3 ± 0·7 cal. mole^{-1} degree^{-1}.



○ *Equilibrium approached from* trans-*side.*
\+ *Equilibrium approached from* cis-*side.*

These values contrast with those for the isomerism of geometrically isomeric hydrocarbons in the gaseous phase where the *cis* to *trans* change is usually slightly exothermic and ΔS almost zero (Table 1).

TABLE 1. *Values of* ΔH, ΔG (*cal./mole*), *and* ΔS (*cal. mole*$^{-1}$ *degree*$^{-1}$) *for the isomerisation of geometrically isomeric hydrocarbons,* cis *to* trans, *in the gas phase at* 25° (from " Selected Values of Properties of Hydrocarbons," Nat. Bur. Stand., Washington).

Hydrocarbon	ΔH	ΔG	ΔS
But-2-ene	−1040	− 731	−1·04
Pent-2-ene	− 880	− 598	−0·95
Hex-2-ene	−1000	− 720	−0·95
Hex-3-ene	−1000	− 800	−0·69
1 : 2-Dimethyl*cyclo*pentane	−1710	−1760	+0·16
1 : 3-Dimethyl*cyclo*pentane	− 540	− 540	0·00
1 : 2-Dimethyl*cyclo*hexane	−1870	−1610	−0·86
1 : 3-Dimethyl*cyclo*hexane	+1940	+1550	+1·38
1 : 4-Dimethyl*cyclo*hexane	−1900	−1490	−1·35
Compare also :			
Ethylene dibromide (gas, 150°) *	−130 ± 300	17 ± 40	−0·34 ± 0·8
Ethylene dichloride (gas, 185°) †	+ 723	+500	+0·49
Ethylene dichloride (in benzene, 150°) ‡	+1200	+750	+1·1

* Noyes and Dickinson, *J. Amer. Chem. Soc.*, **1943**, **65**, 1427.
† Wood and Stevenson, *ibid.*, 1941, **63**, 1650.
‡ Wood and Dickinson, *ibid.*, 1939, **61**, 3259 (these values are not sufficiently accurate to be significantly different from those given for the gaseous phase).

The comparatively large positive entropy change during the isomerisation of the *cis*-platinous complex is probably bound up with the large electric dipole moment which is neutralised during the isomerisation. The *cis*-complex is generally insoluble in non-polar or slightly polar solvents, *e.g.*, petroleum or diethyl ether, but dissolves slightly in benzene, possibly because the relatively flat, readily polarisable benzene molecules can

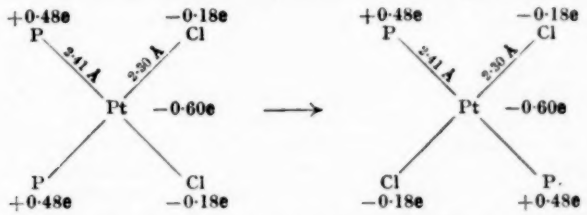
associate with the flat molecule of the complex, and in the intense field of the dipole, become polar. When isomerisation occurs, the large dipole moment of the *cis*-complex is replaced by two smaller opposing moments; these will doubless cause some association of benzene, but smaller than that with the *cis*-isomer. The liberation of the excess of associated benzene would account for the large entropy change during the isomerisation

$$cis\text{-}(PEt_3)_2PtCl_2,nC_6H_6 \rightleftharpoons trans\text{-}(PEt_3)_2PtCl_2,mC_6H_6 + (n - m)C_6H_6$$

If we assume that the entropy of association of the benzene is of the same order as that of freezing benzene (8·55 cal. mole^{-1} degree^{-1}), then the order of $(n - m)$ is $13{\cdot}3/8{\cdot}55 = 1{\cdot}5$, which is reasonable and probably a minimum value.

The heat change during the isomerisation of the *cis*-isomer is made up of three important components: (1) The energy change during the discharge of the electric dipole; (2) the difference in heat of solution of the two isomers from an infinitely dilute gas phase into benzene solution at 25°; (3) the change in bond energy which occurs during isomerisation.

(1) To estimate the first, we know that the interatomic distances in complex compounds of similar types are given sufficiently accurately by the sum of the covalent radii (Mann and Wells, *J.*, 1938, 702), and that the dipole moment of *cis*-$(PEt_3)_2PtCl_2$ in benzene solution is $10{\cdot}7 \times 10^{-18}$ e.s.u. (Jensen, *loc. cit.*). If we assume the Pt–Cl bond moment to be 2×10^{-18} e.s.u., which is a reasonable value [cf. Jensen and Nygaard's value $2{\cdot}5 \times 10^{-18}$ e.s.u. for the Ni–Br bond (*Acta Chem. Scand.*, 1949, **3**, 474)], and also that the smaller PEt_3 moments may be neglected, then the change in the electrical state of the molecule on isomerisation can be represented as in the accompanying scheme.



Using these approximate representations, we calculate the energy dissipated when the *cis*- is converted into the much more favourable *trans*-arrangement to be equivalent to a heat of isomerisation of −15 000 cal./mole.

The charge of −0·60e on the platinum atoms is not in accordance with Pauling's postulate that the resultant electric charge on metal atoms tends to be zero (Contribution to the Study of Molecular Structure, Volume Commémoratif Victor Henri, p. 1, Maison Desoer, Liége, 1947—1948). If we assume it to be zero and attribute all the dipole moment of the *cis*-complex to charges on the phosphorus and chlorine atoms, then each phosphorus atom would have a charge of +0·38e and the chlorine atoms −0·38e. If it is assumed that the charges on these atoms are the same in the *trans*-complex, then the energy dissipated when the *cis*- is converted into the *trans*-complex would be 13 000 cal./mole.

From these two approximations it seems that the loss of electrical energy when the *cis*- is converted into the *trans*-isomer is of the order of 14 000 cal./mole.

We have used the dipole moment measured in benzene solution instead of in the gaseous phase, and assumed the P–Pt–P angle in the *cis*-compound to be 90°, although the repulsion of charges on the phosphorus atoms would make it slightly larger. These will have little effect on the order of the calculated figure, and are compensating errors.

(2) In benzene solution we also have, associated with the *cis*-isomer, the heat of association of the $(n - m)$ molecules of benzene and any heat due to dipole association. Whatever the cause of the observed entropy change of 13·3, the heat associated with it cannot be greater than $13{\cdot}3T = 4000$ cal., which is probably a fair estimate of the maximum value of the second component listed above.

(3) Factors (1) and (2) together would account for a heat of isomerisation of about −10 000 cal. The difference between this and the observed +2500 cal. (*i.e.*, 12 500 cal.)

is thus an approximation to item (3), the difference in total bond energy of the two isomers. We have no means of assessing the error in the figure derived from the above approximations, but even if the electrical energy is wrongly assessed by 50% or 7000 cal., which seems an exaggerated error, the total bond energy of the *cis*- is still higher than that of the *trans*-isomer by at least 5000 cal. and the difference is more probably of the order of 10 000 cal.

All the bonds in both *cis*- and *trans*-isomers are the same, and only the configuration round the platinum atom has changed. Therefore, the large increase in bond energy on converting the *trans*- into the *cis*-complex must arise from placing the phosphorus atoms in *cis*-positions to each other. If *d*-orbitals in the phosphorus and platinum atoms play a part in the binding by π-bonding, then in the *cis*-isomer each phosphorus atom can be bound by a different *d*-orbital in the platinum atom, whereas in the *trans*-isomer each phosphorus atom is competing for the same *d*-orbitals, leading to weaker binding. It follows also that the part played by *d*-orbitals in binding chlorine to platinum must be very different from that in the binding of phosphorus, otherwise placing the chlorine atoms in *trans*-positions to the phosphorus atoms instead of *trans*-position to each other would have led to no increase in bond energy. This correlates with the position of chlorine, which is much lower than phosphorus, in the *trans*-influence series (see Chatt and Williams, *loc. cit.*).

No previous quantitative isomerisation studies of platinous complexes are recorded, but Nikolaev (*Compt. rend. Acad. Sci. U.R.S.S.*, 1938, **20**, 571) noted by plotting heating curves that the isomerisation of solid *cis*-$(NH_3)_2PtCl_2$ is exothermic. *d*-Electrons from the platinum atom can take no part in binding platinum to nitrogen because no 2*d* or other vacant orbitals are available to receive them in the nitrogen atom. From our above study and the *trans*-influence series, *d*-electrons play only a minor part in the binding of chlorine, as compared with phosphorus, to platinum, so we should expect that little energy would be lost by placing the chlorine atoms *trans* to each other. Thus the exothermal change is to be expected in the isomerisation of the *cis*-diammine. However, as the lattice forces are probably much greater in the crystals of the highly polar *cis*-diammine than in its *trans*-isomer, these qualitative measurements are not strictly comparable to our own, which were made in solution. It would be interesting to make isomerisation studies in solution of $(NEt_3)_2PtCl_2$ if such compounds could be prepared, because then we would get some direct measure of the energy to be gained by taking the chlorine atoms from the *trans*- to the *cis*-positions with respect to each other, free from interference by the *trans*-groups.

This study also serves to emphasise the importance of the entropy term in determining the position of equilibrium in reactions involving the formation or destruction of highly polar molecules, and how completely erroneous conclusions regarding relative stability can be arrived at by consideration of only equilibrium positions or decomposition temperatures in the field of co-ordination chemistry.

We are continuing these isomerisation studies to see how different hydrocarbon radicals, acid radicals, and Group V (and VI) elements affect the equilibrium in complexes analogous to $(PEt_3)_2PtCl_2$. Our preliminary survey of the field, so far as platinous complexes are concerned, is summarised in Part III (*J.*, 1951, 2532).

Experimental

cis- and *trans*-Bis(triethylphosphine)dichloroplatinums were prepared like their tri-*n*-propyl homologues (Chatt and Wilkins, *loc. cit.*); they had m. p. 192—193° and 142—143° respectively [Jensen (*Z. anorg. Chem.*, 1936, **229**, 238) gives 191—192° and 142—143°].

Examination of the Isomerisation of cis- *and* trans-$(PEt_3)_2PtCl_2$, *by Separation, Identification, and Weighing of the Products.*—Each pure isomer, in benzene (50 c.c.), was isomerised at 25° by addition of triethylphosphine (0·5 c.c. of M/30-solution). After 30 minutes the equilibrium had been established and was quenched by addition of $(PEt_3)_2Pt_2Cl_4$, sufficient to react with all the free phosphine. This produced mainly a small extra quantity of *trans*-$(PEt_3)_2PtCl_2$, for which allowance was made. The benzene was now evaporated at 15 mm., and the last traces were removed at 0·05 mm. pressure. The pale yellow *trans*-isomer was extracted with ether and decanted from the residue; extraction was repeated until the washings were colourless. The white residue of *cis*-isomer was thoroughly dried at 0·05 mm. pressure and weighed in its tared

container, from which it was removed by washing with acetone. The *trans*-isomer was similarly obtained from its ethereal solution and weighed. The two isomers were then recovered by complete evaporation of the acetone solutions and after drying at 0·05 mm. had the m. p.s, alone and mixed with an authentic specimen, given in Table 2.

TABLE 2.

Wt. of starting material, mg.	Wt. of PEt_3, catalyst, mg.	Wt. of $(PEt_3)_2Pt_2Cl_4$ added to remove catalyst, mg.	Materials recovered from equilibrium mixture: *cis*-compound, mg.	*cis*-compound, m.p.	*cis*-compound, mixed mp.	*trans*-compound, mg.	*trans*-compound, m.p.	*trans*-compound, mixed m.p.	K
	2·0	8·0	0·6	—	—	9·0	—	—	—
cis, 301·0	2·0	9·9	22·6	187—188°	188—189°	292·6	140·5—141·5°	141·5—142·5°	12·9
trans, 306·9	2·0	9·8	22·0	188—189	188·5—189·5	301·8	140·5—141·5	141·5—142·5	13·7
cis, 501·6	1·8	7·1	42·3	186—187	—	473·6	139—140	—	11·2
trans, 507·9	1·8	7·1	42·3	187—188	—	477·6	140—141	—	11·3

Preparation of Dichlorobis(triethylphosphine)-μμ′-dichlorodiplatinum, $(PEt_3)_2Pt_2Cl_4$.—This compound was prepared by heating crude $(PEt_3)_2PtCl_2$ with $PtCl_2$ to 187° for 5 minutes at which temperature considerable blackening occurred (Chatt, *J.*, 1950, 2306); recrystallised from acetone, the orange-yellow *compound* had m. p. 223—224° (Found: C, 18·7; H, 4·0. $C_{12}H_{30}Cl_4P_2Pt_2$ requires C, 18·7; H, 3·9%).

Determination of the Equilibrium Constant (K) *of the Isomerisation Reaction in Benzene Solution.*—*cis*-$(PEt_3)_2PtCl_2$ in benzene solution raises the dielectric constant above that of benzene by about 70 times as much as an equal quantity of the *trans*-isomer. We could thus determine accurately the quantity of *cis*-isomer in presence of its relatively large equilibrium quantity of *trans*-isomer by determining the increase in capacity of an electrical condenser, or cell, when the benzene dielectric, which also contained the catalytic PEt_3, was replaced by the solution under test, in which the total weight of the mixed isomers was known.

The cell used to make these measurements was identical with that of Jenkins and Sutton (*J.*, 1935, 609) except that it was rhodium-plated internally. The changes in capacity of the cell were measured by a heterodyne capacity meter based on that of Hill and Sutton (see *J.*, 1949, 2313). Our standard variable condenser was a Sullivan micrometer condenser of range 5—13 μμF.

The quantities of benzene used in these experiments were those delivered from one particular 50-c.c. graduated flask at the temperature of the determinations, which were at 15°, 43·81 g.; 20°, 43·58 g.; 25°, 43·36 g.; 30°, 43·14 g.; 35°, 42·94 g.

Over the range of concentrations used in these experiments the increase in capacity (ΔC) of the cell, over that with pure benzene as dielectric, was directly proportional to the quantity of added material. At a given temperature when the cell contained a solution of the equilibrium mixture:

$$\Delta C = k_c W_c + k_t W_t + k_p W_p$$

where W_c = weight of *cis*-isomer, W_t = weight of *trans*-isomer, W_p = weight of triethylphosphine present as catalyst, all in the standard quantity of benzene appropriate to the temperature of the determination. At each temperature k_c was determined by making up solutions with W_t and W_p zero, and k_t similarly. As a further check, mixtures of *cis*- and *trans*-isomers were made up and shown to obey the above relationship. Also the addition to the equilibrium mixture of a further quantity of triethylphosphine, equal to that normally used to catalyse the isomerisation, produced exactly the same change in ΔC as when it was added to pure benzene. Thus, to the accuracy of our measurements and at the low concentrations used, the phosphine exists in presence of the platinous complexes in the free state and not as the salt $[(PEt_3)_3PtCl]Cl$ (cf. Nyholm, *J.*, 1950, 848).

To determine the equilibrium constant, a weighed quantity (W) of the appropriate isomer was dissolved in the standard quantity of benzene, containing a trace of triethylphosphine, at the temperature of the determination and transferred to the cell contained in a thermostat. The capacity of the cell changed rapidly until isomerisation was complete (*ca.* 5—20 minutes, depending on the quantity of added phosphine and the temperature). The difference between the final steady capacity and the capacity with the standard volume of benzene containing the

small quantity of phosphine catalyst only, at the same temperature is $\Delta C - k_p W_p$; K was calculated from the equations:

$$\Delta C - k_p W_p = k_c W_c + k_t W_t;\ W = W_c + W_t;\ K = W_t/W_c$$

Because of the inconveniently low solubility of *cis*-$(PEt_3)_2PtCl_2$, most determinations were made by isomerisation of a solution of the very soluble *trans*-isomer, but one sample of *cis*-isomer was isomerised at each temperature. Temperatures were measured with a standardised mercury-in-glass thermometer with accuracy limits $\pm 0{\cdot}02°$. The results are recorded in the following tables.

Values of k_c *and* k_t.

Temp.	W_c, g.	ΔC, $\mu\mu$F	k_c	W_t, g.	ΔC, $\mu\mu$F	k_t
19·85°	0·0366	0·993	27·1	0·4004	0·158	0·395
	0·0396	1·050	26·5	0·5007	0·201	0·401
	0·0431	1·149	26·7			
			(mean 26·8)			(mean 0·398)
24·97	0·0418	1·112	26·6	0·6090	0·231	0·379
	0·0426	1·129	26·5			
	0·0521	1·376	26·4			
	0·0540	1·436	26·6			
			(mean 26·5)			
30·00	0·0390	0·997	25·6	0·5090	0·215	0·422
	0·0420	1·076	25·6	0·6125	0·244	0·398
			(mean 25·6)			(mean 0·410)
35·01	0·0453	1·122	24·8	0·4936	0·198	0·401
	0·0457	1·135	24·8	0·5935	0·231	0·389
	0·0485	1·195	24·6			
			(mean 24·7)			(mean 0·395)

Temp., ° K.	$10^4/T$	W, g.	W_p, g.	$\Delta C - k_p W_p$, $\mu\mu$F	W_c, g.	W_t, g.	K	log K
Isomerisation of trans-$(PEt_3)_2PtCl_2$.								
293·00	34·13	0·4455	0·0020	1·125	0·0359	0·4096	11·4	1·057
		0·4939	0·0020	1·254	0·0401	0·4538	11·3	1·054
		0·5023	0·0020	1·261	0·0402	0·4621	11·5	1·061
298·12	33·54	0·4369	0·0018	1·020	0·0327	0·4042	12·35	1·092
		0·5079	0·0018	1·198	0·0385	0·4694	12·2	1·086
		0·6090	0·0018	1·452	0·0468	0·5622	12·0	1·080
303·15	32·99	0·5090	0·0013	1·109	0·0357	0·4733	13·25	1·123
		0·6003	0·0018	1·314	0·0424	0·5579	13·15	1·119
		0·6125	0·0013	1·333	0·0429	0·5696	13·3	1·123
308·16	32·45	0·4936	0·0009	0·990	0·0327	0·4609	14·1	1·149
		0·5935	0·0009	1·205	0·0399	0·5536	13·9	1·142
Isomerisation of cis-$(PEt_3)_2PtCl_2$.								
293·00	34·13	0·5980	0·0018	1·584	0·0510	0·5470	10·7	1·031
298·12	33·54	0·5016	0·0018	1·238	0·0401	0·4615	11·5	1·061
303·15	32·99	0·5980	0·0018	1·349	0·0438	0·5542	12·6	1·100
308·16	32·45	0·5980	0·0018	1·257	0·0420	0·5560	13·2	1·121

The equilibrium constants at 45° and 60° were determined slightly less accurately by quenching the equilibrium by addition of $(PEt_3)_2Pt_2Cl_4$ and then allowing the mixture to cool to 25° before putting it in the cell. The values of K thus obtained were at 45°, 16·2, and at 60°, 21·2, from the *trans*-side only.

It is to be noted that the equilibrium position is slightly different when approached from the *cis*- as compared with the *trans*-side. The tripropyl complexes show the same effect to a marked extent and in a peculiar manner which will be described in a subsequent communication. As the result of an extensive study of the propyl derivatives, we are convinced that the more accurate value is that obtained by isomerisation of the *trans*-complex. However, even if the values derived from isomerisation of the *cis*-triethylphosphine complex were correct, then the values of $\Delta H = 2470$ cal., $\Delta G = 1395$ cal., and $\Delta S = 13{\cdot}0$ cal. mole^{-1} degree^{-1} derived on this assumption are essentially the same as those quoted, although outside the experimental error. They invalidate in no way the arguments contained in the theoretical part of this communication.

The authors are greatly indebted to Dr. H. Kolsky and Dr. A. R. Miller for valuable discussions, to Mr. D. J. Odds for experimental assistance, and to Miss B. E. Walker for help in carrying out the computations.

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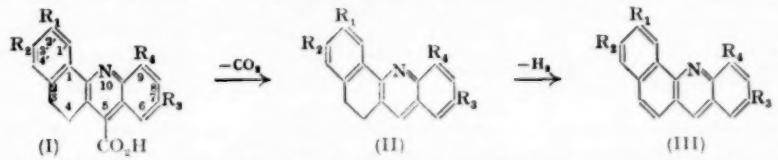
58. *The Chemistry of Carcinogenic Nitrogen Compounds. Part X.* The Pfitzinger Reaction in the Synthesis of* 1 : 2*-Benzacridines.*

By Ng. Ph. Buu-Hoï, Ng. Hoán, and Ng. D. Xuong.

The Pfitzinger–Borsche condensation of isatins with diversely substituted 1-tetralones, followed by decarboxylation of the cinchoninic acids and dehydrogenation of the 3 : 4-dihydro-1 : 2-benzacridines by chloranil, has been successfully employed for the synthesis of several 1 : 2-benzacridines containing methoxy- and halogeno-substituents.

The use of the Pfitzinger–Borsche reaction (Pfitzinger, *J. pr. Chem.*, 1897, **56**, 283; Borsche and Rottsieper, *Annalen*, 1910, **377**, 70) for preparation of 1 : 2-benzacridines was initiated by von Braun and Wolff (*Ber.*, 1922, **55**, 3685; cf. von Braun and Stuckenschmidt, *Ber.*, 1923, **56**, 1727; von Braun, *Annalen*, 1927, **451**, 1), who prepared 3 : 4-dihydro-1 : 2-benzacridine and several of its derivatives by decarboxylation of the corresponding 5-carboxylic acids. Dehydrogenation of the 3 : 4-dihydrobenzacridines was effected by these authors by means of lead oxide at a high temperature, which readily gave 1 : 2-benzacridine itself but brought about the loss of mobile substituents such as chlorine atoms; these observations have recently been confirmed and extended by one of us (Buu-Hoï, *J.*, 1946, 792).

The present work reports the preparation, by the same sequence of reactions, of several new 1 : 2-benzacridines bearing halogen atoms and methoxy-groups, and a modification of the dehydrogenation method, in which chloranil in xylene is used in place of lead oxide. As with carbazole derivatives (Barclay and Campbell, *J.*, 1945, 530) and more complex compounds of the same type (Buu-Hoï, Hoán, Khôi, and Xuong, *J. Org. Chem.*, 1949, **14**, 492; 1950, **15**, 511, 957; 1951, **16**, 315), all the substituents were retained during the dehydrogenation. Thus, 2′-chloro-7-methyl-1 : 2-benzacridine-5-carboxylic acid (I; R_1 = Cl, R_2 = R_4 = H, R_3 = Me), obtained from 7-chloro-1-tetralone and 5-methylisatin,



(I) (II) (III)

gave on decarboxylation 2′-chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine (II; R_1 = Cl, R_2 = R_4 = H, R_3 = Me), and this was smoothly converted by chloroanil into 2′-chloro-7-methyl-1 : 2-benzacridine (III; R_1 = Cl, R_2 = R_4 = H, R_3 = Me); from the same ketone and 5 : 7-dimethylisatin, 2′-chloro-7 : 9-dimethyl-1 : 2-benzacridine (III; R_1 = Cl, R_2 = H, R_3 = R_4 = Me) was similarly synthesised. That both chlorine and bromine atoms are retained in this method is demonstrated by the successful preparation of 7-bromo-2′-chloro-1 : 2-benzacridine (III; R_1 = Cl, R_2 = R_4 = H, R_3 = Br) from 7-chloro-1-tetralone and 5-bromoisatin.

In the group of benzacridines containing methoxy-groups, the present synthesis is a useful alternative to the modified Ullmann–Fettvadjian method (Buu-Hoï, *J.*, 1950, 2096). Thus, 2′-methoxy-1 : 2-benzacridine was readily obtained from 3 : 4-dihydro-2′-methoxy-1 : 2-benzacridine-5-carboxylic acid (I; R_1 = OMe, R_2 = R_3 = R_4 = H) *via* its decarboxylation product. Condensation of 7-methoxy-1-tetralone with isatin had already been performed by von Braun (*loc. cit.*), but the m. p. 123° given for the reaction product was erroneous; dehydrogenation of 3 : 4-dihydro-2′-methoxy-1 : 2-benzacridine could also be effected through the lead monoxide method. When, however, alkyl groups were present simultaneously, the chloranil method was far superior, as in the case of 2′-methoxy-3′ : 7-dimethyl-1 : 2-benzacridine (III; R_1 = OMe, R_2 = R_3 = Me, R_4 = H), prepared from 7-methoxy-6-methyl-1-tetralone and 5-methylisatin.

* Part IX, *J.*, 1951, 2964.

During this work, several other 3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acids were also prepared from 1-tetralones, and some of the decarboxylation products were isolated, but further study was discontinued because the 1 : 2-benzacridines were not carcinogenic.

Experimental

2'-Chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine-5-carboxylic Acid.—7-Chloro-1-tetralone, m. p. 96°, was prepared from chlorobenzene by the standard succinic anhydride method; von Braun (*loc. cit.*) prepared it by a Sandmeyer reaction from the diazo-compound from 7-aminotetralone and gave m. p. 94°. A solution of 7-chloro-1-tetralone (2 g.), 5-methylisatin (2 g.), and potassium hydroxide (2 g. in 2 c.c. of water) in ethanol (10 c.c.) was refluxed for 24 hours on a water-bath. After dilution with water (50 c.c.), removal of neutral impurities by ether-extraction, and acidification with acetic acid, an *acid* (3·5 g.) was precipitated, crystallising as fine, pale yellow needles, shrinking above 200°, m. p. 269°, from toluene (Found : C, 70·1; H, 4·5. $C_{19}H_{14}O_2NCl$ requires C, 70·5; H, 4·3%).

The pale yellow *acids* recorded in the table were similarly prepared.

R_1	R_2	R_3	R_4	Yield, %	M. p.	Crystal form	Solvent	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
Substituted 3 : 4-*dihydro*-1 : 2-*benzacridine*-5-*carboxylic acids* (I).														
Cl	—	Me	Me	70	246°	Needles	PhMe	$C_{20}H_{16}O_2NCl$	70·8	4·5	—	71·1	4·7	—
Cl	—	Br	—	90	319	Prisms	EtOH	$C_{18}H_{11}O_2NBrCl$	55·2	3·0	—	55·6	2·8	—
MeO	—	—	—	90	229	Prisms	MeOH	$C_{19}H_{15}O_3N$	—	—	4·6	—	—	4·6
MeO	Me	Me	—	—	256	Needles	EtOH	$C_{21}H_{19}O_3N$	75·4	5·6	—	75·7	5·7	—
MeO	Me	—	—	—	264 [a]	Needles	EtOH	$C_{20}H_{17}O_3N$	75·0	5·4	—	75·4	5·3	—
MeO	MeO	—	—	—	263–264	—	EtOH	$C_{20}H_{17}O_4N$	71·4	5·0	—	71·6	5·1	—
—	MeO	—	—	95	329	Needles	Xylene	$C_{19}H_{15}O_3N$	—	—	4·4	—	—	4·6
—	MeO	Me	—	90	319	—	—	$C_{20}H_{17}O_3N$	—	—	4·3	—	—	4·4
—	MeO	Br	—	80	308	Prisms	AcOH	$C_{19}H_{14}O_3NBr$	59·1	3·4	—	59·4	3·6	—
[a] Solvated crystals melt at <200°.														
Substituted 3 : 4-*dihydro*-1 : 2-*benzacridines* (II).														
Cl	—	Me	Me	—	99°	Prisms [1]	EtOH–C_6H_6	$C_{19}H_{16}NCl$	77·4	5·7	—	77·6	5·4	—
Cl	—	Br	—	—	122	Needles [2]	EtOH	$C_{17}H_{11}NBrCl$	59·1	3·1	—	59·2	3·2	—
MeO	—	—	—	—	82	Leaflets [3]	EtOH	$C_{18}H_{15}ON$	82·4	5·9	—	82·7	5·7	—
MeO	Me	Me	—	—	129	Needles [4]	EtOH	$C_{20}H_{19}ON$	83·1	6·9	—	83·0	6·6	—
MeO	Me	—	—	—	109	Needles [5]	EtOH	$C_{19}H_{17}ON$	82·6	6·4	—	82·9	6·2	—
MeO	MeO	—	—	—	114–115	Needles [6]	EtOH	$C_{19}H_{17}O_2N$	—	—	4·7	—	—	4·8
—	MeO	—	—	—	90	Needles [7]	EtOH	$C_{18}H_{15}ON$	82·5	6·0	—	82·7	5·7	—
—	MeO	Me	—	—	107	Needles [8]	EtOH	$C_{19}H_{17}ON$	82·5	6·2	—	82·9	6·2	—
—	MeO	Br	—	—	151	Prisms [9]	C_6H_6	$C_{18}H_{14}ONBr$	63·2	4·2	—	63·5	4·1	—
MeO	—	Br	—	—	158	Needles	EtOH	$C_{18}H_{14}ONBr$	—	—	4·0	—	—	4·1

[1] Picrate, m. p. 143°. [2] Picrate, m. p. 236°. [3] Picrate, m. p. 231°. [4] Pale yellow; picrate, m. p. 254°. [5] Yellow; *picrate*, prisms (from EtOH), m. p. 242° (Found : N, 11·4. $C_{25}H_{20}O_8N_4$ requires N, 11·1%). [6] Pale yellow; picrate, m. p. 227°. [7] Picrate, m. p. 211°. [8] Picrate, m. p. 216°. [9] Yellow.

2'-Chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine.—The well-dried corresponding carboxylic acid (2 g.) was heated above its m. p. in a vacuum, and the residue distilled. The distillate (1·2 g.) formed fine shiny, colourless needles, m. p. 129°, from ethanol (Found : C, 77·0; H, 5·1. $C_{18}H_{14}NCl$ requires C, 77·2; H, 5·0%), and gave a picrate crystallising as fine shiny yellow prisms, m. p. 233°, from ethanol. Decarboxylation of the other acids gave yields ranging from 60% (for the halogen-containing acids) to 90%.

The *dihydro*-compounds tabulated were similarly prepared.

2'-Chloro-7-methyl-1 : 2-benzacridine.—A solution of the corresponding dihydro-compound (0·5 g.) and chloranil (1 g.) in dry xylene (10 c.c.) was refluxed for 48 hours. After cooling and filtration, and repeated washing of the filtrate with dilute aqueous sodium hydroxide, then with water, the xylene was evaporated, and the residue crystallised as silky pale yellow needles (0·3 g.), m. p. 141°, from ethanol (Found : N, 4·9. $C_{18}H_{12}NCl$ requires N, 5·0%); the corresponding *picrate* crystallised as fine, deep yellow needles, m. p. 247°, from ethanol (Found : N, 11·2. $C_{24}H_{15}O_7N_4Cl$ requires N, 11·0%). All the other dehydrogenations gave the following products in excellent yield ranging from 70 to 90% (pure) :

2'-Chloro-7 : 9-dimethyl-1 : 2-benzacridine formed pale yellow shiny leaflets, m. p. 162°, from benzene (Found : N, 4·6. $C_{19}H_{14}NCl$ requires N, 4·8%). *7-Bromo-2'-chloro-1 : 2-benz-*

acridine formed almost colourless needles, m. p. 192°, from benzene (Found: N, 4·0. $C_{17}H_9NBrCl$ requires N, 4·1%); the orange-yellow picrate had m. p. 235°. ***2′-Methoxy-1 : 2-benzacridine*** formed pale yellow prisms, m. p. 128°, from ethanol (Found: C, 83·3; H, 5·0. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). ***2′-Methoxy-3′ : 7-dimethyl-1 : 2-benzacridine*** crystallised as silky, almost colourless needles, m. p. 159°, from ethanol (Found: N, 4·8. $C_{20}H_{17}ON$ requires N, 4·9%).

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59. *Rate-determining Factors in Certain* ortho-*Nitrations.*

By J. C. D. BRAND and R. P. PATON.

The relative velocities of nitration of *p*-X·C_6H_4·NO_2 and *p*-X·C_6H_4·NMe_3^+ (X = Me, Bu^t, Cl, Br, and H) have been measured in sulphuric acid solution. Halogen and alkyl substituents reduce the relative velocity, $k_{NO_2}/k_{NMe_3^+}$, compared with the unsubstituted compounds, and this effect is discussed in terms of the differential interaction of the substituent with the remainder of the system. The velocity coefficients for nitration of *p*-Hal·C_6H_4·NO_2 are in the order Br > Cl > F, and this may represent the order of electromeric polarisability of the halogen atom in these molecules.

A *p*-METHYL substituent reverses the comparative ease of sulphonation (in fuming sulphuric acid) of the systems C_6H_5·NO_2 and C_6H_5·NMe_3^+, the order of reactivity being *p*-Me·C_6H_4·NMe_3^+ > *p*-Me·C_6H_4·NO_2 ≫ C_6H_5·NO_2 > C_6H_5·NMe_3^+. The results, at 25°, are (Brand, *J.*, 1950, 997, 1004):

(*a*) *p*-Me·C_6H_4·NO_2 and (*b*) *p*-Me·C_6H_4·NMe_3^+: $k_{(a)}/k_{(b)} = 0·8$ (*c*) C_6H_5·NO_2 and (*d*) C_6H_5·NMe_3^+: $k_{(c)}/k_{(d)} = 1·5$

These figures, however, were obtained indirectly. In the media employed, the nitro-compounds were converted almost quantitatively into the conjugate ions, Ar·NO·OH^+, and it was necessary to allow for this before comparing the experimental velocities. The accuracy with which this was possible was low. The degree of conversion was, in general, too high to be measured directly and was evaluated from the ionisation constant of the nitro-compound and the acidity function of the medium. Furthermore, the relative velocity coefficients above were calculated on the assumption that the ions were unreactive and that sulphonation occurred entirely through the small, equilibrium concentration of *un-ionised* base. The kinetic evidence for this assumption was discussed in the original paper but, if it is correct, similar velocity ratios would be expected to hold for other substitution reactions. Partly as a test of this, the relative rates of nitration of systems of the same type have now been measured in 90—96% sulphuric acid. In this solvent the degree of ionisation of the nitro-compounds is negligibly small. The results have confirmed the analysis of the sulphonation experiments.

Effect of p-*Substituents on the Relative Rate of Nitration of* C_6H_5·NO_2 *and* C_6H_5·NMe_3^+.—The relative velocities were, for the most part, measured competitively and are collected in Table 1. *Relative* nitration velocities are approximately independent of medium composition (Bonner, James, Lowen, and Williams, *Nature*, 1949, **163**, 955) and temperature (for small differences) and the results in the table may be compared with one another directly. *p*-Nitrotoluene and *p-tert.*-butylnitrobenzene were not completely un-ionised in the media employed, but the concentration immobilised in this way (*ca.* 3—4 moles %) was low enough to be neglected for our purpose. With the exception of nitrobenzene,

nitration occurs quantitatively in position 3, *i.e.*, *ortho* to the substituent X, if one is present.

Nitrobenzene yields about 92% of *m*-dinitrobenzene (Pounder and Masson, *J.*, 1934, 1352) and the relative velocity in Table 1 refers to nitration in the 3-position only. The fact that nitrobenzene and the phenyltrimethylammonium ion are nitrated at similar speeds is, of course, fortuitous, for the character of the two substituents is entirely different.

TABLE 1. *Relative velocities of nitration of* p-X·C_6H_4·NO_2 *and* p-X·C_6H_4·NMe_3^+ *in sulphuric acid.*

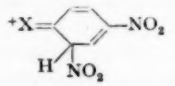
	Temp. 25°				Temp. 18°	
Substituent, X	H	Cl		Br	Bu^t	Me
Medium, % H_2SO_4	90·7	90·7	89·8	89·8	95·8	95·3
k_{NO_2}	1·7	1·1$_5$	—	—	0·5$_2$	0·3$_2$
$k_{NO_2}/k_{NMe_3^+}$	1·9 *	—	1·22 *	1·19 *	—	—

* Ratio of velocity coefficients (Table 2). The value for X = H in this row is from Bonner, James, Lowen, and Williams (*loc. cit.*).

The relative rate of nitration, $k_{NO_2}/k_{NMe_3^+}$, is a maximum for the unsubstituted compounds; it is lowered by halogen and alkyl substituents, and the latter produce the inversion already encountered in sulphonation. The important fact for the interpretation of this behaviour is that the halogen and alkyl substituents *both* reduce the relative rate. Because alkyl groups in all circumstances release electrons, this suggests that the explanation must be connected also with the electron-releasing properties of the halogen. The principal effect of the latter is to lower the energy of the transition state, provided the carbon atom at which substitution takes place is conjugated to the halogen. The primary factor determining the relative velocity is probably located, therefore, in the transition state of the nitration. The argument will be illustrated with reference particularly to *p*-chloronitrobenzene and the ion *p*-Cl·C_6H_4·NMe_3^+. The structure (I; X = Cl) is known, *e.g.*, from the following dipole-moment data (in D)

p-Cl·C_6H_4·NO_2; μ = 2·78, calc. 2·52 : cf. *m*-Cl·C_6H_4·NO_2; μ = 3·69, calc. 3·68

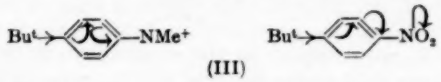
to contribute appreciably to the complete wave function of *p*-chloronitrobenzene in the normal state. The interaction between the substituents must exist also in the collisionally excited state although it may alter in magnitude. In the transition state of nitration (Hughes, Ingold, *et al.*, *J.*, 1937, 1257; 1941, 608; Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; Dewar, *J.*, 1949, 463) this conjugation between the substituents will compete with important resonance structures such as (II; X = Cl) and thus reduce the stabilisation afforded by the chlorine atom. The essential assumption is that this conjugation is much

(I)  (II)

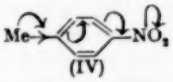
more imperfectly developed in the ion *p*-Cl·C_6H_4·NMe_3^+, because the NMe_3^+ group is purely inductive, and interference with the normal function of the halogen in the transition state is correspondingly smaller. The same view is expressed in the statement that the *p*-NO_2 group (compared with NMe_3^+) more effectively reduces the electromeric polarisability of the chlorine atom, because the halogen surrenders a greater electron density to the nitro-group and is, therefore, less polarisable in the field of the attacking nitronium ion.

The argument for the *p*-Bu^t compounds, although the substituent is inductive, must be similar. For our purpose it is unnecessary to distinguish between transmission along the σ-bonds or through the unsaturation electrons and both are referred to as inductive or inductomeric effects of the Bu^t group. The "inverted" reactivities are thought to arise partly from a greater inductomeric polarisability of the Bu^t substituent in the ion *p*-Bu^t·C_6H_4·NMe_3^+. This results, much as in the previous case, from the diminution of the polarisability of the alkyl group owing to the loss of electrons by the processes represented

in (III), which proceed further in the nitro-compound than in the quaternary ammonium ion. However, an additional factor operating in the same direction will be discussed below. In the systems with a *p*-methyl substituent (which have also been discussed by Lowen, Murray, and Williams, *J.*, 1950, 3318), hyperconjugation and induction act in co-operation (IV) and the greater differential effect further lowers the relative rate.



(III)



(IV)

The explanation of why the alkyl groups depress the relative rate of nitration more than do the halogens is perhaps as follows. Although only the differential effect of the $\cdot C_6H_4\cdot NO_2$ and $\cdot C_6H_4\cdot NMe_3^+$ system on the substituent has been discussed hitherto, the differential effect of the substituent on the rest of the system is also significant. The point in question is the extent to which $\cdot C_6H_4\cdot NO_2$ and $\cdot C_6H_4\cdot NMe_3^+$ polarise in the field of different substituents, and we assume that the former, having the greater conjugation path, polarises more, *i.e.*, that NO_2, compared with NMe_3^+, will smooth out differences of electron density at the point of substitution caused by substituents elsewhere in the ring. If this is accepted, taken by itself it means that an activating substituent will decrease the relative rate, $k_{NO_2}/k_{NMe_3^+}$ (because more of the electrons released by the substituent accumulate in the nucleus linked to the quaternary nitrogen atom) and that a deactivating substituent will increase it. This effect does not involve the nitronium ion explicitly and is not confined to collisionally activated states; neither is it the whole truth because it must operate simultaneously with the effects considered previously. It is the resultant that is significant. With alkyl substituents the two factors co-operate to reduce the relative rate, whereas with the halogens they are in opposition.

Influence of Polarisability on Nitration Velocity.—The influence of halogens on the velocity of nitration in the *p*-nitrophenyl series can be seen from the results in Table 2.

TABLE 2. *Nitration of derivatives of* $Ph\cdot NO_2$ *and* $Ph\cdot NMe_3^+$ *in* H_2SO_4 (Temp. 25°).

	Initial concn. (moles/l.) of: ArH	HNO_3	Medium, % H_2SO_4	k_2 (mean) †
p-$Cl\cdot C_6H_4\cdot NMe_3^+$	0·005	0·094	89·8	0·340
p-$Br\cdot C_6H_4\cdot NMe_3^+$	0·004	0·094	89·8	$0{\cdot}71_2$
p-$Cl\cdot C_6H_4\cdot NO_2$	0·001	0·094	89·8	$0{\cdot}41_4$
p-$Br\cdot C_6H_4\cdot NO_2$	0·001	0·094	89·8	0·85
p-$F\cdot C_6H_4\cdot NO_2$	0·002	0·084	90·6	$0{\cdot}06_9$
$C_6H_5\cdot NO_2$ *	—	—	90·0	4·6
	—	—	95·5	1·8
p-$Me\cdot C_6H_4\cdot NO_2$	0·00024	0·00030	95·5	590
	0·00025	0·001	99·0	240 (300)
p-$Bu^t\cdot C_6H_4\cdot NO_2$	0·00016	0·001	99·0	33·2 (45)

* Bonner, James, Lowen, and Williams, *loc. cit.*

† k_2 is given in the units $min.^{-1}$ $mole^{-1}$ l.

Values of the velocity coefficients given in parentheses (99% H_2SO_4) are calculated on the *molecular* concentration of nitro-compound, to correct for ionisation.

Measurements with *p*-iodonitrobenzene were impracticable because of the insolubility and ease of decomposition; otherwise the order in which the halogens were effective in retarding nitration was F > Cl > Br. This differs from the known influence of halogens in the simple halogenobenzenes (Table 3), especially in the case of fluorine, and the new order is presumably the result of the modifying influence of the nitro-group. A plausible explanation is that we are observing the order of electromeric polarisability of the halogens, the mesomeric effect having become subordinate. The conjugation between the halogen and the nitro-group (I) is presumably responsible for this, because electrons are transferred in this way from one substituent to the other without activating the nucleus. The order of electromeric polarisability, F < Cl < Br, is the same as that deduced by Bird and Ingold (*loc. cit.*) from reaction (2) (Table 3), in which the electromeric and mesomeric effects are thought to be of comparable importance.

Finally, it is interesting to note the quantitative influence of methyl and halogen substituents on nitration velocity in the nitrophenyl series. Methyl being compared with chloro-, for example, nitration is, respectively, accelerated 330-fold and retarded 11-fold (Table 3). By combining the results in Tables 1 and 2 it can be seen that corresponding substitutions in the quaternary ammonium ion systems increase the disparity. This behaviour is consistent with our view that the nitration velocity of these highly electron-deficient systems is determined by polarisability factors which would enhance the reactivity of the substituted, with respect to the unsubstituted, systems. Unfortunately, to compare the ratios above with those observed for reactions of simple monosubstituted benzenes, it is necessary to assume that the physical effect of the change of solvent can be neglected; this being granted, our nitrations closely resemble the chlorination, but not the nitration, of PhX. The substituent effects in chlorination of the phenyl halides are also thought (de la Mare, *J.*, 1949, 2871) to show that the influence of polarisability is relatively important; however, in this case the electron-demanding character of the reaction is due primarily to the nature of the *reagent*, and the order in which the halogens are effective in retarding chlorination is, therefore, normal.

TABLE 3. *Relative effect of methyl and halogen substituents on the speed of nuclear substitution.*

	Medium		Substituent, X						
Reaction	Solvent	Temp.	Me	H	F	Cl	Br	I	Ref.
(1) *o*-Nitration of PhX	Ac_2O	18°	43	1·0	0·05	0·030	0·034	0·2	1, 2
(2) Overall nitration of PhX ...	Ac_2O	18	25	1·0	0·15	0·033	0·030	0·18	1, 3
(3) Overall chlorination of PhX	AcOH $+H_2O$	24	350	1·0	1·2	0·11	0·079	—	4
(4) Nitration of *p*-X·C_6H_4·NO_2	H_2SO_4 $+H_2O$	25	330	1·0	0·015	0·090	0·185	—	Table 2

1, Bird and Ingold, *J.*, 1938, 918. 2, de la Mare and Robertson, *J.*, 1948, 100. 3, Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959. 4, de la Mare and Robertson, *J.*, 1943, 276; de la Mare, *loc. cit.*

EXPERIMENTAL

Materials.—p-*Bromo-*, p-*chloro-* and p-tert.-*butyl-phenyltrimethylammonium methyl sulphate* were prepared from the corresponding tertiary amine and methyl sulphate in acetone, and purified by recrystallisation from slightly aqueous acetone. They had, respectively, m. p. 121° (also 138°) (Found: C, 36·9; H, 4·6; N, 4·3. $C_{10}H_{16}O_4NBrS$ requires C, 36·8; H, 4·9; N, 4·3%), m. p. 143° (Found: C, 42·5; H, 5·7; N, 5·2. $C_{10}H_{16}O_4NClS$ requires C, 42·6; H, 5·7; N, 5·0%), and m. p. 214° (Found: C, 56·0; H, 8·2; N, 4·7. $C_{14}H_{25}O_4NS$ requires C, 55·5; H, 8·3; N, 4·6%).

p-*tert.*-Butylnitrobenzene, m. p. 28·3° after fractional solidification, and 1-*tert.*-butyl-2 : 4-dinitrobenzene, m. p. 62°, were prepared by nitration of *tert.*-butylbenzene (cf. Craig, *J. Amer. Chem. Soc.*, 1935, **57**, 195). Other compounds employed were: *p*-bromonitrobenzene, m. p. 126°; *p*-chloronitrobenzene, m. p. 83·5°; *p*-fluoronitrobenzene, m. p. 26·8°; nitrobenzene, m. p. 5·7°; *p*-nitrotoluene, m. p. 52°; phenyltrimethylammonium methyl sulphate, m. p. 126°; *p*-tolyltrimethylammonium methyl sulphate, m. p. 144° (m. p.s are uncorrected).

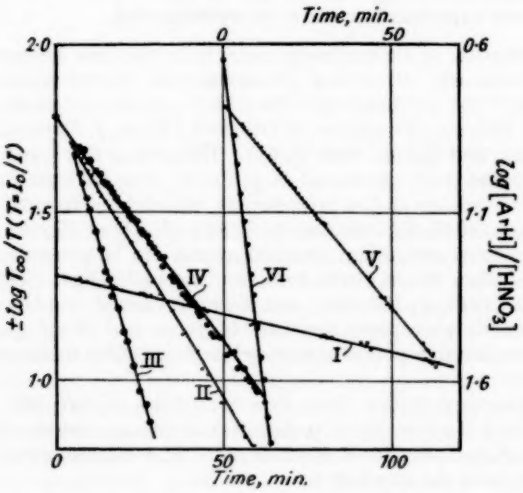
Competitive Nitrations.—In these experiments the product was analysed by measuring the optical density of the solution after nitration, at a wave-length of 3650 Å, a Hilger " Spekker " Absorptiometer being used. The method was to allow a mixture of nitro-compound and quaternary ammonium salt to compete in sulphuric acid solution for nitric acid, all at suitable, known initial concentrations, and subsequently to measure the transmission of diluted samples. This procedure was possible because the nitrations were known to yield one product only, and because the nitration of the nitro-compound brought about a very large change (*ca.* ten-fold in favourable media) of extinction coefficient. Essentially, the optical measurement was an analysis for the mononitro-compound, which was the only strongly absorbing constituent of the solution at the wave-length employed; for this reason, two nitro-compounds or two quaternary ions were not compared directly by the competitive method. The calculation of the relative velocity (Bird and Ingold, *loc. cit.*), from the initial concentrations and the optical density of the nitrated solution, is illustrated by the results in Table 4. The sum of the errors

TABLE 4. *Relative velocity of nitration of* p-$Bu^t \cdot C_6H_4 \cdot NO_2$ *and* p-$Bu^t \cdot C_6H_4 \cdot NMe_3^+$ *in* 95·8% H_2SO_4 (Temp. 18°).

p-tert.-Butylnitrobenzene, $\varepsilon = 6200$; 1-*tert.*-butyl-2 : 4-dinitrobenzene, $\varepsilon = 610$; 1-*tert.*-butyl-2-nitrophenyltrimethylammonium ion, $\varepsilon = 385$ (cm. mol./kg.)$^{-1}$.

	Initial concn. $\times 10^3$ (molal) (A)	Dilution ratio and optical density (after nitration)	Final concn. $\times 10^3$ (molal) (B)	log A/B	$\frac{k_{NO_2}}{k_{NMe_3^+}}$
(*a*) $Bu^t \cdot C_6H_4 \cdot NO_2$ ...	4·662	30·40 × 0·665	(*a*) 2·905	(*a*) 0·206	—
(*b*) $Bu^t \cdot C_6H_4 \cdot NMe_3^+$	4·650	—	(*b*) 1·744	(*b*) 0·426	0·48
(*c*) KNO_3	4·663	—	—	—	—
(*a*) As above	4·801	30·21 × 0·668	(*a*) 2·967	(*a*) 0·209	—
(*b*) ,, ...	4·782	—	(*b*) 1·852	(*b*) 0·412	0·51
(*c*) ,, ...	5·764	—	—	—	—
Second analysis :					
(*a*)	4·801	31·60 × 0·627	(*a*) 2·905	(*a*) 0·218	—
(*b*)	4·782	—	(*b*) 1·915	(*b*) 0·397	0·54
(*c*)	4·764	—	—	—	—
(*a*)	2·342	14·66 × 0·779	(*a*) 1·523	(*a*) 0·187	—
(*b*)	6·977	—	(*b*) 3·110	(*b*) 0·351	0·53
(*c*)	4·688	—	—	—	—
(*a*)	6·966	43·24 × 0·621	(*a*) 3·925	(*a*) 0·249	—
(*b*)	2·392	—	(*b*) 0·758	(*b*) 0·499	0·50
(*c*)	4·676	—	—	—	—

(about ±2 parts %) in the optical measurements corresponded to about ±10 parts % in the relative rate, depending on the amount by which the extinction coefficients fell during nitration. In the case of *p*-chloronitrobenzene, the change which occurred in the nitration medium itself (90·7% H_2SO_4) was too small, and the solution was analysed by dilution with 15·7% fuming sulphuric acid (103·5% H_2SO_4) in which the much more strongly absorbing conjugate cation was formed. A similar procedure was adopted with nitrobenzene and *p*-nitrotoluene.



(a) *Apparent first-order coefficients (left-hand and bottom legends).*
(b) *Second-order coefficients (right-hand and top legends).*

I, p-$F \cdot C_6H_4 \cdot NO_2$ (90·3% H_2SO_4).
II, p-$Cl \cdot C_6H_4 \cdot NO_2$ (89·8% H_2SO_4).
III, p-$Br \cdot C_6H_4 \cdot NO_2$ (89·8% H_2SO_4).
IV, p-$Cl \cdot C_6H_4 \cdot NMe_3^+$ (89·8% H_2SO_4).
V, p-$Bu^t \cdot C_6H_4 \cdot NO_2$ (99·0% H_2SO_4).
VI, p-$Me \cdot C_6H_4 \cdot NO_2$ (99·0% H_2SO_4).

A fully nitrated solution of *p*-chloronitrobenzene (nitration at 25° in 90·7% H_2SO_4) was found to have the same extinction coefficient [$\varepsilon = 1923$ (cm.mol./kg.)$^{-1}$ in 103·5% H_2SO_4] as a solution of 1-chloro-2 : 4-dinitrobenzene in the same medium ($\varepsilon = 1928$). This test was also applied satisfactorily to *p-tert.*-butylnitrobenzene and 1-*tert.*-butyl-2 : 4-dinitrobenzene [$\varepsilon = 610$ (nitrated) and 595 (cm.mol./kg.)$^{-1}$ respectively in 95·8% H_2SO_4].

Velocity Measurements.—Nitration velocities were determined from the rate of change of optical density at 3650 Å. The reaction proceeded in optical cells (depth, 1 cm.) immersed in a water thermostat at 25°. Media were prepared by dissolving potassium nitrate in sulphuric

acid, the low concentration of potassium hydrogen sulphate liberated having no appreciable effect on the nitration velocity (Bennett *et al.*, *J.*, 1947, 474). The initial concentration of nitratable material was 10^{-2}—10^{-4} molar, depending on the intensity of absorption. *p*-Iodonitrobenzene was too insoluble and too easily decomposed to be investigated in this medium. For nitration of the *p*-halogen derivatives of nitrobenzene and the phenyltrimethylammonium ion, the nitric acid concentration was in invariant excess and the reaction of first order. This condition could not be preserved with the reactive alkylbenzenes, for which second-order velocity coefficients were evaluated directly (see figure, where $\log T_\infty/T = \log I/I_\infty \propto [\mathrm{ArH}]$). Except for the most rapid reactions, the substances were added as solids to the nitrating mixture, the quaternary ammonium salts being introduced as their methyl sulphates.

Microanalyses were carried out by Miss R. H. Kennaway.

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60. *Determinations of Electrokinetic Charge and Potential by the Sedimentation Method. Part I. Silica in Aqueous Solutions of Potassium Chloride.*

By C. I. DULIN and G. A. H. ELTON.

The sedimentation method for the determination of electrokinetic charges and potentials is applied to the study of fused silica surfaces in dilute aqueous potassium chloride solutions. The results obtained are in good agreement with those calculated from streaming potentials, confirming that the basic assumptions used in deriving the theory of the method are sound. Addition of small amounts of silver chloride to the solutions produces a rise in the charge and a fall in the potential, indicating that the use of silver–silver chloride electrodes in electrokinetic experiments is not to be recommended.

VARIOUS methods exist for the determination of electrokinetic potentials, the best known being from measurements of electro-osmosis, streaming potential, and cataphoresis. However, as a general rule, the values of the potential determined for a given system by the different methods are very different (see, *e.g.*, Monaghan, White, and Urban, *J. Physical Chem.*, 1935, **39**, 585; White, Monaghan, and Urban, *ibid.*, p. 611; Rutgers and de Smet, *Trans. Faraday Soc.*, 1945, **41**, 758). The poor agreement is probably due, at least in part, to weakness in the theory of electro-osmosis and of cataphoresis, pointed out recently by Overbeck and Wijga (*Rec. Trav. chim.*, 1946, **65**, 556) and by Booth (*J. Chem. Physics*, 1950, **18**, 1361), respectively. The theory of streaming potential appears to be generally accepted, at least in the case of wide tubes where electroviscosity has little effect (see, *e.g.*, Elton and Hirschler, *Proc. Roy. Soc.*, 1949, *A*, **198**, 581), and the most careful measurements of electrokinetic potentials yet made were probably those of Jones and Wood (*J. Chem. Physics*, 1945, **13**, 106), using the streaming potential method for fused silica surfaces in aqueous potassium chloride solutions.

Recently, a new method has been proposed (Elton, *Proc. Roy. Soc.*, 1949, *A*, **197**, 568; *J. Chem. Physics*, 1951, **13**, 1317) in which the velocity of sedimentation of suspensions of small particles of the solid in the solutions considered is observed. The electrokinetic charge may then be calculated directly from the expression

$$\sigma^2 = g\kappa(u_0 - u)(\rho_2 - \rho_1)/MA_0{}^2uu_0\rho_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where σ = charge (e.s.u.) per unit area on the particles immersed in the given solution; g = gravitational constant; κ = specific conductivity (e.s.u.) of the suspension; u_0 = rate of settling of the suspension in the absence of electroviscosity (*i.e.*, in a concentrated electrolyte solution); u = rate of settling of the suspension in the given solution; ρ_2, ρ_1 = densities of particles and of solution, respectively; M = mass of particles per ml. of suspension; A_0 = area per g. of particles.

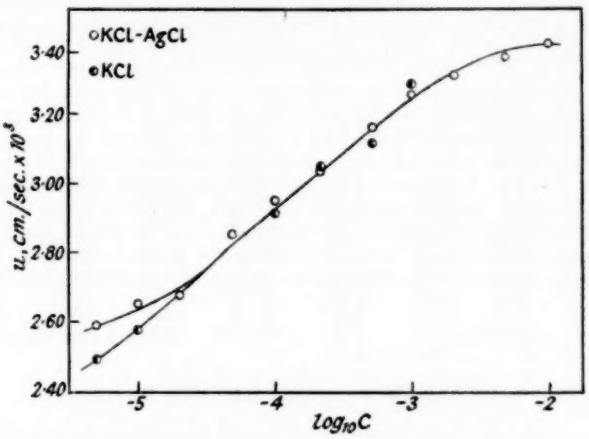
When the charge has been determined, the electrokinetic potential is obtained by using Verwey and Overbeck's expression ("Theory of the Stability of Lyophobic Colloids," 1948, Elsevier Publ. Co. Inc., London), *viz.*,

$$\sigma = \left(\frac{2n\varepsilon kT}{\pi}\right)^{\frac{1}{2}} \sinh\left(\frac{ze\zeta}{2kT}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where n = number of charge-determining ions per ml. of the solution; ε = dielectric constant in the electrical double layer; k = Boltzmann constant; T = absolute temperature; z = valency of charge-determining ion; e = charge on the electron; ζ = electrokinetic potential.

Two difficulties, the first of which is inherent in all electrokinetic calculations, arise in the use of equation (2): (*a*) ε, the dielectric constant in the double layer may differ from the bulk value of the dielectric constant, owing to the high electric field in the vicinity of the surface, though this effect is likely to be small for solutions of concentration up to about 10^{-3}N (Conway, Bockris, and Ammar, *Trans. Faraday Soc.*, 1951, **47**, 756). (*b*) In aqueous solutions, ions of several kinds may be present, *viz.*, ions of added electrolyte, together with hydrogen and hydroxyl ions, and also bicarbonate ions unless very careful

Sedimentation velocities.



precautions to exclude carbon dioxide are taken. Further ions may be provided by ionisation of the solid surface although this source may be neglected for the purpose of the present paper, where work on fused silica surfaces is to be described. (The case of a solid, *i.e.*, glass, which ionises to some extent, is to be dealt with in a later paper in this series.) The number of hydrogen, hydroxyl, and bicarbonate ions present in conductivity water is small, but at very low concentrations of added electrolyte, say below 10^{-5}N, equation (2) is not strictly applicable, since it was derived for a single electrolyte species.

Since an assumption concerning the value of ε is necessary for all calculations of electrokinetic potentials (see Wood, *J. Amer. Chem. Soc.*, 1946, **68**, 432), it would in any case seem preferable to leave all data in terms of electrokinetic charge, a quantity which can be determined unambiguously from measurements of sedimentation velocity, using equation (1). Most data in the literature are, however, given in terms of electrokinetic potential, so in this paper values of both quantities are given. It appears likely from the above discussion that the potentials calculated are reasonably accurate in the concentration range 10^{-5}N to 10^{-3}N, *i.e.*, for most of the range over which electrokinetic measurements are usually required. In order to test this conclusion, determinations have been carried out for the system fused silica–aqueous potassium chloride solution, since silica provides a reproducible surface which is easily cleaned and, as mentioned above, reliable values for the electrokinetic potentials in this system are available for comparison from the work

of Jones and Wood. One criticism can, however, be made of this work, *viz.*, that in measuring the streaming potentials, use was made of silver–silver chloride electrodes. Our experiments have shown that these electrodes are not suitable for use in very dilute potassium chloride solutions, as the ionic concentrations may be appreciably increased by dissolution of silver chloride from the electrodes. In order to allow for this, sets of experiments were carried out by use of (i) plain potassium chloride solutions and (ii) potassium chloride solutions saturated with respect to silver chloride.

The sedimentation velocities obtained for a particle-sized specimen of fused silica powder in the two sets of experiments are shown graphically in the figure. In the table, data taken from the smoothed curves have been used to calculate surface charges and potentials, $n = n_{Cl^-}$ being used for the latter calculation; *i.e.*, allowance has been made for the extra ions present in the solutions containing silver chloride. In the table, u_1, κ_1, σ_1, ζ_1, refer to the plain potassium chloride solutions, and u_2, κ_2, σ_2, ζ_2, to the solutions with added silver chloride. Jones and Wood's values are given in the last column. It is seen that the effect of the silver chloride is to raise the charge and lower the potential at low potassium chloride concentrations. The agreement between ζ_2 and Jones and Wood's values is quite good, being of the order of 5%, much better than that usually found between two independent methods. [For example, Rutgers and de Smet (*loc. cit.*) determined ζ for a given glass in potassium chloride solutions from measurements of both streaming potential and electro-osmosis. They found that the latter method gave potentials consistently about 30% lower than the former.]

Concn., N	$\kappa_1 \times 10^6$	$\kappa_2 \times 10^6$	$u_1 \times 10^3$	$u_2 \times 10^3$	$\sigma_1 \times 10^{-2}$	$\sigma_2 \times 10^{-2}$	ζ_1	ζ_2	ζ (J. & W.)
1×10^{-2}	1460·88	1460·88	$3{\cdot}41_0$	$3{\cdot}41_0$	77·20	77·20	79·3	79·3	—
5×10^{-3}	730·88	730·88	$3{\cdot}37_0$	$3{\cdot}37_0$	65·73	65·73	88·2	88·2	—
2×10^{-3}	292·88	292·88	$3{\cdot}30_7$	$3{\cdot}30_7$	51·29	51·29	98·5	98·5	—
1×10^{-3}	146·8	146·8	$3{\cdot}24_1$	$3{\cdot}24_1$	42·30	42·30	106·2	106·2	112·5
5×10^{-4}	73·9	73·9	$3{\cdot}16_0$	$3{\cdot}16_0$	34·83	34·83	113·8	113·8	—
2×10^{-4}	30·8	30·8	$3{\cdot}05_9$	$3{\cdot}05_9$	26·03	26·03	122·3	122·3	—
1×10^{-4}	15·28	15·50	$2{\cdot}94_3$	$2{\cdot}94_3$	21·00	21·15	129·0	129·0	133·6
5×10^{-5}	8·18	8·58	$2{\cdot}85_0$	$2{\cdot}85_0$	16·85	17·26	135·5	135·3	—
$2{\cdot}5 \times 10^{-5}$	4·53	5·21	$2{\cdot}73_8$	$2{\cdot}73_8$	13·85	14·85	143·2	142·0	—
2×10^{-5}	3·80	4·55	$2{\cdot}70_2$	$2{\cdot}70_2$	13·07	14·30	146·0	143·9	—
1×10^{-5}	2·34	3·24	$2{\cdot}58_4$	$2{\cdot}64_0$	11·23	12·57	156·0	146·0	142·0
5×10^{-6}	1·51	2·51	$2{\cdot}46_3$	$2{\cdot}58_7$	9·795	11·61	167·0	147·6	—
$1 \times$	—	—	$3{\cdot}50_2$	$3{\cdot}50_2$	—	—	—	—	—
Water *	—	—	—	—	—	—	—	—	177·0

* See Wood, *J. Amer. Chem. Soc.*, 1946, **68**, 437.

It therefore appears that for the concentration range 10^{-5}N to 10^{-3}N, the only one covered by Jones and Wood's work, the error introduced by setting n in equation (2) equal to the chloride-ion concentration, is small. Further tests, over wider ranges of concentration, are desirable, and are being made by us, but as previously mentioned, few reliable data for comparison are available. The good agreement between the results obtained from streaming potential and sedimentation velocity is some confirmation that the theoretical basis of the methods is sound. The latter method is a simple one to carry out experimentally, provided that the material to be studied is obtainable in powder form in sufficient quantity to permit the extraction of a 50—100 mg. sample of uniform particle size.

Finally, we may conclude from the differences obtained in the two sets of experiments that for electrokinetic measurements, the use of silver–silver chloride electrodes is not to be recommended, at least in dilute solutions. This was realised by Wood and Robinson (*J. Chem. Physics*, 1946, **14**, 258), who used bright platinum electrodes for their measurements on silica in dilute solutions of barium chloride.

Experimental

Materials.—Fused silica powder was supplied by Messrs. Thermal Syndicate Ltd. It was cleaned by repeated boiling with aqua regia, and washed many times with conductivity water. The water used throughout these experiments had a conductivity of 0·6—0·8 gemmho, similar

to that used by Jones and Wood. Potassium chloride was obtained by recrystallising the "AnalaR" salt several times from conductivity water. Silver chloride was prepared from recrystallised "AnalaR" silver nitrate by reaction in dilute solution with the calculated quantity of potassium chloride, washed thoroughly, and used immediately.

Particle Sizing of Silica.—This was done by fractional sedimentation in a number of large shallow pans followed by a similar process in measuring cylinders. The specimen used in the experiments described, weighing about 70 mg., was separated from about 100 g. of powder. It formed a suspension which sedimented at a uniform rate, giving a sharp settling meniscus with a limiting rate of fall, in concentrated solutions, of $3{\cdot}50 \times 10^{-3}$ cm./sec.

Sedimentation Experiments.—The specimen of silica was suspended in 100 ml. of aqueous potassium chloride solution, and the sedimentation experiments carried out as described previously (Elton, 1949, *loc. cit.*), in a thermostat at 25·00° ± 0·01°. Solutions were prepared by successive dilution, after the suspension had been allowed to settle out, at least two determinations being made at each concentration. The weight of particles per ml. in the suspension was determined at the completion of the series by centrifuging and weighing on a microbalance: $M = 6{\cdot}765 \times 10^{-4}$ g./ml.

Surface-area Determination.—This was done by a modification of the catalytic decomposition method described by Elton and MacDougall (*J. Soc. Chem. Ind.*, 1946, **65**, 212). A known weight of the particles was given a very thin continuous coating of metallic silver by stirring them for ten minutes in ammoniacal 4% silver nitrate solution at 60—70°. The silvered particles were then washed, with centrifuging, and transferred to a flask containing 100 ml. of a borax buffer solution of pH 9·7 in a thermostat at 25·00°. The suspension of particles was stirred, and 25 ml. of 0·1N-hydrogen peroxide solution at 25·00° rapidly introduced into the flask. At the end of 100 seconds, the reaction was stopped by the addition of an excess of 2N-sulphuric acid, and the hydrogen peroxide remaining determined by titration with permanganate. The rate of decomposition of the peroxide is directly proportional to the surface area of silver present. The method was standardised by using a silvered specimen of glass microspheres, prepared by Bloomquist and Clark's method (*Ind. Eng. Chem. Anal.*, 1940, **12**, 61), and accurately particle-sized by the method described above. Determinations of limiting settling rate and weight per ml. of a suspension of the glass spheres gave their mean radius and area per g. The surface area of the silica was then obtained by comparing the rates of decomposition of the peroxide by the two silvered materials. Area per g. $(A_0) = 1{\cdot}234 \times 10^4$ cm.^{2}.

BATTERSEA POLYTECHNIC, S.W.11. [*Received, September 12th*, 1951.]

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61. *Some N-Substituted Derivatives of Poly-α-aminoacrylic Acid.*

By MAX FRANKEL and MANFRED E. REICHMANN.

Poly-α-carbobenzyloxyaminoacrylic acid, poly-α-formamidoacrylic acid and its methyl ester, and poly-α-carbethoxyaminoacrylic acid have been prepared by polymerisation of suitable monomers. Removal of the protecting group attached to the α-amino-group of these polymers has not yet been realised.

IN an attempt to synthesise polyelectrolytes containing in each unit both the amino- and the carboxy-group, the polymerisation of certain derivatives of α-aminoacrylic acid has been studied. As starting materials the following derivatives were used: α-carbobenzyloxyamino- (I) and α-formamidoacrylic acid (II) [and its methyl ester], and αα-di-(carbethoxyamino)propionic acid (III).

The acid (I) was prepared from αα-di(carbobenzyloxyamino)propionic acid (Martell and Herbst, *J. Org. Chem.*, 1941, **6**, 878) by treatment with hot glacial acetic acid (cf. Bergmann and Grafe, *Z. physiol. Chem.*, 1930, **187**, 187). The acid (III) was obtained by condensation of urethane with pyruvic acid. Preparation of (II) from α-formamidolactic acid was reported by Shive and Shive (*J. Amer. Chem. Soc.*, 1946, **68**, 117); we prepared (II) by condensation of formamide and pyruvic acid under conditions set out in the Experimental section, isolation of the lactic acid being unnecessary; the yields in our method are lower

but the procedure is more convenient. Esterification of (II) was carried out with methyl sulphate as described by Rothstein (*J.*, 1949, 1968) for the corresponding *N*-acetyl compound.

$CH_2{:}C(CO_2H)\cdot NH\cdot CO\cdot O\cdot CH_2\cdot C_6H_5$ (I) $CH_2{:}C(CO_2H)\cdot NH\cdot CHO$ (II) $CH_2\cdot C(CO_2H)(NH\cdot CO_2Et)_2$ (III)

Polymerisation experiments with (I) and (II) were carried out in *NN*-dimethylformamide at 60° with benzoyl peroxide as catalyst, and at 0° with toluene-*p*-sulphinic acid as catalyst (Hagger, *Helv. Chim. Acta*, 1948, **31**, 1624). The products constituted white hard materials, insoluble in water and the usual organic solvents. The molecular weight of a polymer obtained from (I) (benzoyl peroxide as catalyst) was found to be about 30,000 by light scattering (solution in *NN*-dimethylformamide). The intrinsic viscosity in this solution was 0·13 (concn. in g./100 ml.). Toluene-*p*-sulphinic acid gave a polymer of (I) having in *NN*-dimethylformamide an intrinsic viscosity of 0·51. When (III) was heated above its melting point, a polymer was obtained, the analysis of which was in agreement with the formula of poly-α-carbethoxyaminoacrylic acid. Apparently the monomer formed under these conditions by elimination of one mole of urethane immediately polymerised. The monomer could not be isolated by treating (III) with hot glacial acetic acid. The poly-α-carbethoxyaminoacrylic acid was dissolved in methanol and precipitated with ether. It is soluble in methyl, as well as in ethyl, alcohol and slightly soluble in water. The intrinsic viscosity in methanol solution of this polymer was 0·58. Potentiometric titration in aqueous solution gave the form of curve characteristic for hysteresis, indicating strong aggregation in which the functional carboxylic groups were involved. In conformity with this, addition of alkali beyond the equivalent point caused a drop in relative viscosity as a consequence of the breakdown of aggregates.

With the polymer obtained from (I) with benzoyl peroxide as catalyst, experiments were carried out to remove the carbobenzyloxy-group by catalytic hydrogenolysis, by reduction with phosphonium iodide, and by acid or alkaline hydrolysis. None of these methods has so far been successful. Difficulties in the removal of this group from polymeric peptides were encountered also by other workers (Frankel and Katchalski, Sci. Papers pres. to Ch. Weizmann, 1944, **24**, 74; Katchalski, Grossfeld, and Frankel, *J. Amer. Chem. Soc.*, 1947, **69**, 2564; 1948, **70**, 2094; Hanby, Waley, and Watson, *J.*, 1950, 3239). Poly-α-formamido- and poly-α-carbethoxyamino-acrylic acid were not hydrolysed by acid or alkali. Similar difficulties are reported by Adams and his co-workers (*J. Amer. Chem. Soc.*, 1950, **72**, 5080) in a paper which appeared after the experiments presented here were concluded ; these authors failed to remove the acetyl groups from poly-α-acetamido-acrylic acid and ascribe the resistance to hydrolysis of the polymer to lactam formation.

Experimental

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

α-Carbobenzyloxyaminoacrylic Acid.—αα-Di(carbobenzyloxyamino)propionic acid (50 g.) (Martel and Herbst, *loc. cit.*) in glacial acetic acid (250 ml.) was boiled under reflux for 3 minutes and then cooled as quickly as possible. The cooled solution was poured into ice-water (1·5 l.) with vigorous stirring. A yellow oil separated which solidified after 10—20 minutes. The mixture was left in the ice-box overnight, then filtered, and the solid material extracted repeatedly with four 20-ml. portions of ice-cold sodium hydroxide solution (3%). The combined filtrates were acidified with concentrated hydrochloric acid with cooling and stirring. The slightly yellow oil which separated upon acidification solidified at once. It was left overnight in the ice-box and then filtered off. The white powder was dried in a desiccator over concentrated sulphuric acid (yield, 53%) and recrystallised twice from toluene. The *α-carbobenzyloxyaminoacrylic acid* was insoluble in water, slightly soluble in benzene and toluene, and soluble in alcohol, ethyl acetate, ether, acetone and dioxan. It melts at 105° with decomp. (Found : C, 60·1; H, 5·3; N, 6·4. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

Polymerisation. The acid (5 g.) and benzoyl peroxide (150 mg.) were dissolved in *NN*-dimethylformamide (15 ml.), and nitrogen was passed through the solution for 20 minutes. The vessel was sealed and left for 12 hours in a thermostat at 60°. The *poly-α-carbobenzyloxyaminoacrylic acid* was precipitated from the highly viscous solution by addition of ether and

filtered off. It was a white, hornlike material, soluble in glacial acetic acid and *NN*-dimethylformamide, insoluble in water and the common organic solvents. It was dissolved in *NN*-dimethylformamide and reprecipitated with ether, then dried in a vacuum (yield, 4·4 g.) (Found : C, 60·1; H, 5·2; N, 6·7%).

The monomer (0·5 g.) and toluene-*p*-sulphinic acid (15 mg.) were dissolved in *NN*-dimethylformamide (1·5 ml.), and nitrogen was passed through the solution for 10 minutes. The vessel was sealed and kept in an ice-bath for 12 hours. The polymer was precipitated and washed as in the foregoing experiment.

α-Formamidoacrylic Acid.—Anhydrous formamide (10 g.) and freshly redistilled pyruvic acid (20 g.) were heated at 70° under an air condenser at 30 mm. After about 2 hours white crystals were precipitated. The heating was continued for an additional hour. The flask was then cooled and left overnight in the ice-box. The solidified mixture was washed with small quantities of cold water and filtered with suction. The crystalline material obtained (2·6 g.), recrystallised from ethanol, decomposed at 170° (Found : C, 41·9; H, 4·3; N, 12·0. Calc. for $C_4H_5O_3N$: C, 41·7; H, 4·4; N, 12·2%).

Unsaturation was determined with Dam's reagent; 96% and 95% of the theoretical value were obtained.

Polymerisation. A mixture of the monomer (0·5 g.), benzoyl peroxide (15 mg.), and *NN*-dimethylformamide (1·5 ml.) was deaerated and sealed under nitrogen. After 2 hours at 60° a slight turbidity was perceptible. Within 12 hours at 60° the *polymer* was precipitated; it was washed with *NN*-dimethylformamide and ether (Found : C, 41·4; H, 4·2; N, 12·0%).

Methyl α-Formamidoacrylate.—Formamidoacrylic acid (2 g.) was suspended in methanol (35 ml.), and a 6% sodium methoxide solution in methanol was added drop by drop until all the acid had dissolved. Quinol (0·3 g.), sodium carbonate (1 g.), methyl sulphate (3 g.), and one drop of methyl-orange were added and the mixture was heated on the water-bath for 2 hours, during which a small quantity of sodium carbonate was added from time to time to maintain alkalinity. The solution was then cooled, dry ether was added, and the precipitated sodium salts were filtered off. The ether was evaporated *in vacuo*. The remaining viscous oil was distilled under reduced pressure, giving *methyl α-formamidoacrylate* (60—70%), m. p. 53° b. p. 87°/5 mm. (Found : C, 46·5; H, 5·5; N, 10·9. $C_5H_7O_3N$ requires C, 46·5; H, 5·4; N, 10·9%).

Polymerisation. (i) This was carried out in *NN*-dimethylformamide as for the acid. The polymer was precipitated from the viscous solution by water and the hornlike substance was filtered off, dried, and powdered. It was insoluble in the usual organic solvents.

(ii) A mixture of the ester (1 g.) and benzoyl peroxide (10 mg.) in a test-tube was heated at 60° for 12 hours. A yellow brittle glass was obtained.

αα-Di(carbethoxyamino)propionic Acid.—Urethane (25 g.) and freshly distilled pyruvic acid (13 g.) were heated under an air-condenser at 80°/25—30 mm. for 3 hours. Then it was cooled in ice–salt, and cold water (10 ml.) was added. After vigorous stirring, the oil solidified. It was left overnight in the ice-box, then filtered off and washed with a small quantity of cold water. The white crystalline material (55%) was dried over concentrated sulphuric acid in a desiccator.

αα-Di(carbethoxyamino)propionic acid, recrystallised from ethyl acetate, had m. p. 120° (Found : C, 43·7; H, 6·5; N, 11·0. $C_9H_{16}O_6N_2$ requires C, 43·6; H, 6·5; N, 11·3%).

Poly-α-carbethoxyaminoacrylic Acid.—The foregoing acid (2 g.) was heated at 125° for 1 hour, giving a yellow gel which was dissolved in methanol (5 ml.) and precipitated by ether (25 ml.). The white amorphous precipitate was centrifuged, redissolved in methanol, and reprecipitated with ether. After centrifugation, the *poly-α-carbethoxyaminoacrylic acid* was powdered and dried *in vacuo* (yield, 30%). It is soluble in alcohol and acetone, slightly soluble in water [Found : C, 44·9; H, 5·8; N, 8·9. $(C_6H_9O_4N)_n$ requires C, 45·3; H, 5·7; N, 8·8%].

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JERUSALEM, ISRAEL. [*Received, September 18th*, 1951.]

62. *Electron Distribution in Conjugated Free Radicals.*

By JULIANE JACOBS.

In the two systems $CH_{3-x}Ph_x$ and $CH_{3-x}(C_6H_4Ph)_x$ the free-valence numbers are deduced from an investigation of bond orders as defined in the molecular-orbital theory. The corresponding quantities arising in certain *p*-benzoquinone dimethides are also reported. On the basis of these data, changes in aromatic character of the hexagons under increasing phenylation are observed and the diradical behaviour of certain meriquinones is discussed. The results are correlated with predictions of reactivity ascribed to the presence of free electrons.

SYSTEMS with one unpaired electron are usually free radicals. Two types of radicals may be distinguished by the degree of mobility of their unpaired electron: (i) if the electron is more or less localised, the reactivity is mostly concentrated at one centre, as in alkyl radicals; (ii) if the electron is free to move over part or all of the molecule the reactivity will be correspondingly spread out. We are concerned only with conjugated hydrocarbon radicals in which the odd electron moves in a π-type orbital extending over the whole carbon framework. In so far as reactivity is governed by properties of the conjugation electrons, all electrons in such π-type orbitals must evidently be taken into consideration.

It seems desirable to introduce some differentiation between the several meanings attached to the word reactivity. Indeed it may be necessary to distinguish between the various reactivities of an atom, expressed by its readiness to participate in reactions, relative to other centres in the same molecule, or to corresponding centres in related molecules. Again the reaction rates may refer to a specific reagent, a single group or a conjugating system, to homolytic or heterolytic substitutions. In no way can it be claimed that the present methods of calculation are adequate to deal with these several reactivities; but the two theoretical quantities, free-bonding power and electron density, may be correlated with two different aspects of reactivity.

To some extent the reactivity of an atom in a molecule is governed by the number and type of bonds in which this atom participates. In the theory of molecular orbitals (M.O.) this has been measured by a free-valence number defined as the potential bonding power not already engaged in bond formation. We may therefore expect that the free valence at an atom is an indicator of its readiness to undergo homolytic reactions. Likewise the electron density at an atom, as defined in the molecular-orbital theory, may be expected to serve as a rough index of the ability of an atom to take part in heterolytic reactions.

Using the molecular-orbital technique we have investigated the dependence of free-valence values on the environment within a particular compound, and have applied our considerations to the phenyl-, $CH_{3-x}Ph_x$, and diphenylyl-methyls, $CH_{3-x}(C_6H_4Ph)_x$. As the two series of compounds are closely allied, changes in free valence may be observed not only from atom to atom within one molecule, but also between corresponding atoms of the two groups. The other quantity that has a bearing on reactivity is the odd-electron density, for which we have established values at all carbon atoms. This seemed worthwhile not only to discover variations in the availability for ionic reactions, but also for the sake of a comparison with predictions made on the basis of the valence-bond (V.B.) theory. For these molecules, results of valence-bond calculations are available (Pullman, *Discuss. Faraday Soc.*, 1947, **2**), some of which are reproduced below. All these radicals have one non-bonding orbital with zero orbital energy which is occupied in the ground state by just one unpaired electron. (The value of the Coulomb integral for a $2p_z$-electron is taken as zero on this scale.) This electron of zero orbital energy is not concerned with bonding and may therefore be associated with the "free" electron of the conventional bond diagrams. In the molecular-orbital theory this electron is not confined to one single carbon centre but has a distribution over the whole framework; this distribution is recorded below as the odd-electron density.

A comparison of molecular-orbital (M.O.) and valence-bond (V.B.) results has been given for some radicals (Moffitt and Coulson, *Trans. Faraday Soc.*, 1948, **44**, 81). In their work, Pauling, Brockway, and Beach's (*J. Amer. Chem. Soc.*, 1935, **57**, 2705) formula for bond orders was used, which is unsatisfactory as the free-bonding power depends on the initial choice of canonical structures (Daudel, Jacques, Jean, Sandorfy, and Vroelant, *J. Chim. phys.*, 1949, **46**, 249). It is, however, more readily adapted to include unpaired electrons than the more consistent Penney–Dirac (*Proc. Roy. Soc.*, 1937, *A*, **158**, 306) formula for bond orders. By means of the latter substantial agreement with calculations by the molecular-orbital method is reached for bond orders in conjugated hydrocarbons.

It is also the purpose of these calculations to follow the effect of increasing phenylation on the electron density at the methyl carbon; the latter being the site of the free electron in the conventional bond diagram for these radicals. Our numerical results will make more precise the correlation that exists between the conventional structural diagrams and theoretical predictions.

Method and Results

The molecular-orbital method was applied in its simplest form with neglect of all overlap integrals and with equality of all resonance integrals, approximations which are insignificant in a discussion of free valence (Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265). The bond orders of all bonds were then determined by the standard technique (see *e.g.*, Coulson, *Quart. Reviews*, 1947, **1**, 44). In molecular-orbital theory the total bonding of an atom r is denoted by :

$$N_r = \sum_s p_{rs} + C_r$$

where C_r = number of σ-bonds concurrent at atom r, s = a neighbouring carbon atom, and p_{rs} = mobile order of the bond r–s. The free valence at atom r is then defined in terms of the maximum potential bonding power as :

$$\text{free valence} = N_{\max.} - N_r = 4{\cdot}732 - N_r$$

The value of the constant $N_{\max.}$ has been given by Coulson as 4·680 for the condensed polynuclear hydrocarbons. Recently Moffitt (*Trans. Faraday Soc.*, 1949, **45**, 373) has obtained the value $3 + \sqrt{3} = 4{\cdot}732$ for the hypothetical radical $C(CH_2)_3$, which value we adopt for our discussion. It has been found (Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 533) that for certain purposes it is better to use different values of $N_{\max.}$ according as the relevant carbon atom is a primary, secondary, or tertiary one. In the present discussion, however, we have used the tertiary value $N_{\max.} = 3 + \sqrt{3}$ throughout both for simplicity and for convenience; for it seemed desirable to include CH_3 in the comparison and this would not fit immediately into the above authors' scheme.

The diagrams (Figs. 1 and 2) show values of bond orders along bonds, free valences on arrows, and odd-electron densities at atoms. Values at positions not marked follow from symmetry. Hydrogen atoms are omitted altogether. In Fig. 3 fractional orders of bonds are represented schematically. Only portions of molecules are shown; values at the remaining portions again follow from symmetry. The diagrams of Fig. 4 allow a comparison of V.B. and M.O. results for free valence at the methyl carbon. These V.B. results were published by Pullman (*loc. cit.*) (P.B.B. denotes that Pauling, Brockway, and Beach's definitions of bond orders were used to determine free valences).

Extension to Diradicals.—The determination of free valence from calculated bond orders has also been carried out for certain meriquinones. Some of these compounds may exist as diradicals but at low temperatures they exist in a singlet diamagnetic state.

Fig. 5 shows *p*-benzoquinone dimethide (I) and its diradical (II) which have been discussed by Coulson, Craig, Maccoll, and Pullman (*Discuss. Faraday Soc.*, 1947, **2**). For (I) they find the free valences of the ring nuclei are much the same as in benzyl or diphenylyl; but the values of free valence at the end carbon nuclei are unusually high, as for a free radical. If the molecule were originally formed as the diradical (II) it would be in a triplet state, the two free electrons having unpaired spins. For this form of the molecule the above authors report free valences differing little from those of (I). They conclude therefore that the triplet is not much more reactive than the singlet ground state.

We extend our considerations to the more complex compounds of meriquinone type, *G*, *H*, *J*, *K*, in order to investigate how far we are justified in describing them as diradicals. The

FIG. 1.

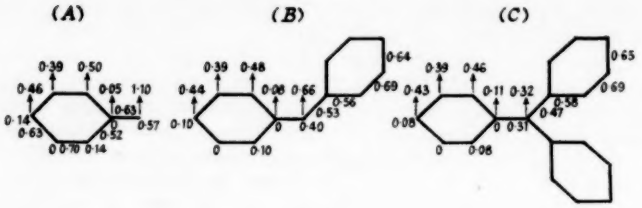


FIG. 2.

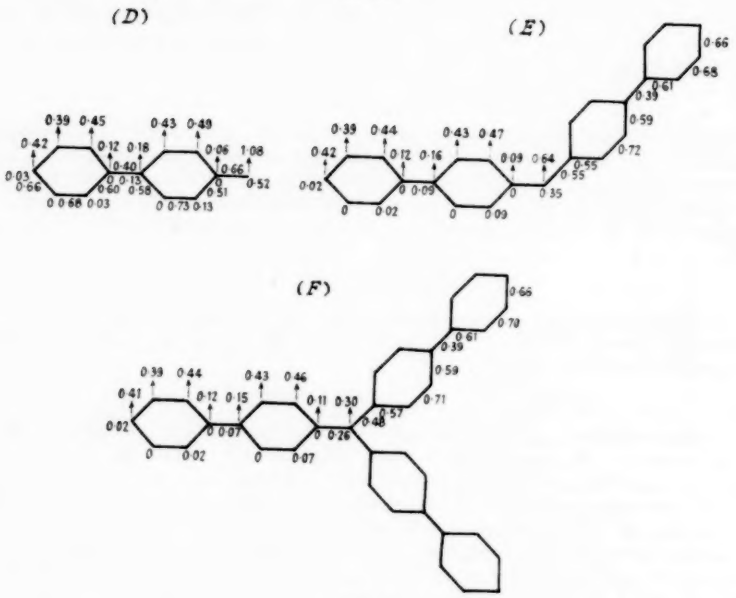
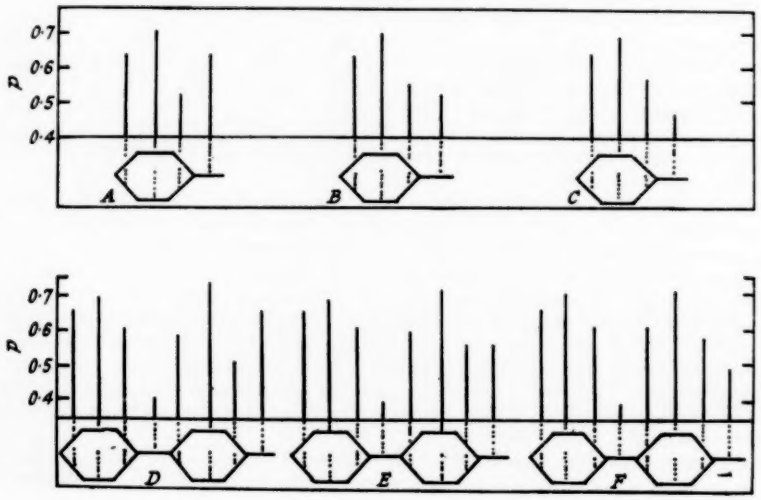


FIG. 3.



calculated bond orders will decide whether the hexagons should be of quinonoid or benzenoid type. The nature of these rings will in turn determine whether the structural diagram requires an odd electron on the methyl carbon; for if the central ring has an aromatic bond diagram, a free electron is required as in (II), which does not arise from a quinonoid ring as in (I). The greater reactivity at the methyl carbon atom may be due to a pair of loosely bound electrons,

FIG. 4.

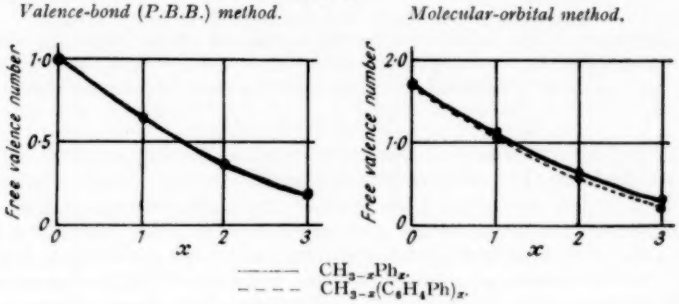


FIG. 5.

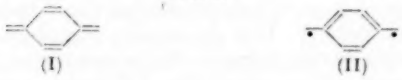
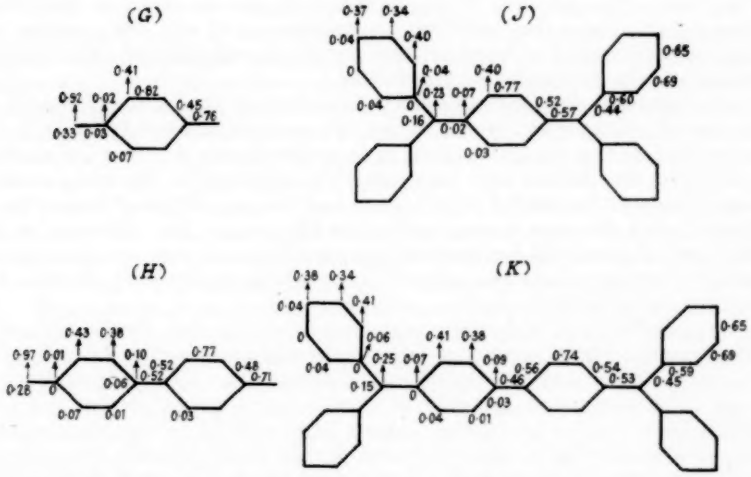


FIG. 6.



in the sense in which it depends on the odd electron in a free radical. However, in terms of the M.O. treatment, the odd electron in a free radical is clearly distinguished from other conjugation electrons by having an orbital energy value $\varepsilon = 0$, which cannot arise in these compounds. Each of the molecules *G* to *K* contains an even number of mobile electrons, the energy value $\varepsilon = 0$ does not occur, in the ground state all bonding orbitals are doubly filled, and all anti-bonding orbitals are empty. Nevertheless, a level with a small ε value exists in all four compounds; this means they each have a pair of electrons whose spins are paired but whose binding energy is approximately zero. These electrons do not actively participate in bonding but behave rather like isolated electrons. To this extent they can be associated with the odd electron pair shown in (II) (Fig. 5). We have therefore calculated the probability distribution of the pair of π-electrons with small orbital energy.

For compounds *G* and *H* similar results for bond orders and free valence according to the

M.O. method have already been published by Pullman and Pullman (*J. Chim. phys.*, 1949, **46**, 212). These authors demonstrated also how, with increasing conjugation, *i.e.*, increasing the number of double bonds through a series of similar compounds, the maximum value of free valence may increase or decrease according to the particular way in which hexagons are added to the simpler radicals.

The compounds investigated are shown schematically in Fig. 6, the positions of carbon atoms only being indicated. Again the bond orders are shown along bonds, free valences on arrows, and electron densities of the nearly non-bonding electrons at atoms.

In these calculations the molecules have been assumed planar, although steric hindrance to planarity certainly exists. Consequently our calculated values must not be given an absolute significance, but should be considered as giving relative values only among these compounds.

Discussion

(a) *Substituted Methyl Radicals.*—The older theory of reaction ascribed the reactivity of a radical to the presence of an odd electron at a specific centre. This is clearly inadequate, for it is a characteristic property of the radicals under discussion that their reactivity is not localised at one particular atom. According to the M.O. theory, no π-electron is thus confined, but rather all conjugation electrons are treated as moving in orbitals extending over the whole molecule, *i.e.*, they are given a certain probability density at all atoms. In alternant hydrocarbons (Coulson and Rushbrooke, *Proc. Camb. Phil. Soc.*, 1940, **36**, 193), the electron density in the ground state is uniformly unity and therefore can give no indication of a varying reactivity. We may associate the " free " electron with the non-bonding one found in M.O. theory. It is the density distribution of this electron which would be expected to give a better estimate of the reactivity than is derived from the picture of a free electron confined to a single site. This zero-energy electron has assumed further significance since Longuet-Higgins (*loc. cit.*) has recently predicted that a close parallelism must exist between charge distributions due to unpaired electrons of zero orbital energy and those obtained from a consideration of only the principal resonance structures. He pointed out, however, that usually calculations of odd-electron density will be more effective for predicting reactivities.

Our calculations of odd-electron density show that its alternating character, observed in chain molecules with an odd number of carbon atoms, persists in these radicals. Starting from the methyl carbon the odd electron is to be found only on alternate nuclei, but the uniformity of its distribution over these centres is destroyed. The odd-electron density shows a maximum at the methyl carbon atom, and the probability of finding this electron on alternate nuclei decreases as we recede from this atom. The odd-electron density at the methyl carbon atom also decreases with increase in x, *i.e.*, with increasing phenylation. Furthermore, there is a slight reduction in this electron density with the transition from phenylmethyls to diphenylylmethyls.

No exact parallelism exists between variations in odd-electron density and free valence. However, throughout both systems of radicals there is a comparatively high free valence and odd-electron density at the methyl carbon atom with relatively low values at all its neighbours. The decrease in odd-electron density at the methyl carbon is accompanied by a simultaneous reduction in free valence there. Thus in the simpler structures, $x = 1$, the free valence has a maximum value for the whole molecule there, but its value is diminished rapidly with the passage to the more complex molecules in the group.

The loss in free valence at the methyl nucleus in passing through both the phenyl and the diphenylyl series from $x = 1$ to $x = 3$ is to some extent compensated by a slight increase in free valence at atoms which are its nearest neighbours, where the free valence is consistently low. In the near rings of *A*, *B*, and *C* the free valences have closely similar values with a minimum at the *meta*-positions. A similar minimum occurs at the carbons in the *meta*-positions in the outer rings of *D*, *E*, and *F*; however, the total variations in free valence in these rings are small, both within each hexagon and within the whole group of diphenylyl compounds. Approaching the rings from the methyl carbon atom we find an extremely low free valence on the first ring nuclei. In *D*, *E*, and *F* the free valences decrease considerably in passing along each hexagon away from the methyl carbon, and the values again lie close to one another in all three compounds.

The overall picture is the close similarity of the variations in free valence within the phenyl- and the diphenylyl-methyls. In both groups the initially outstanding value of free valence at the methyl carbon atom is decreased rapidly through approximately the same sequence of numerical values, as phenylation is increased.

The calculated bond-order distribution may be related to the classical structural diagrams for these compounds by following the changes in fractional bond order around the rings. If the variations in bond-order values around a conjugated ring are small, we have a situation rather as in benzene, where, according to the M.O. theory, all bonds have a fractional mobile order $p = 2/3$. The conventional way is, however, to show a benzene ring with three double and three single bonds alternating with one another. A quinonoid hexagon is suggested by a bond order which for the central bonds is nearly double and greatly exceeds the orders of the end bonds of the ring.

The actual values as well as the variations in bond order within the near rings are very similar in the phenyl and diphenylyl compounds (Fig. 3). In each group for $x = 1$ the changes of bond order inside a ring are large, suggesting four single and two double central bonds; for $x = 3$ the values in the near rings have become more nearly uniform and are, numerically also, close to the corresponding bond orders in benzene. Increased phenylation modifies therefore the quinonoid nature of the first rings to a benzenoid one. The quinonoid quality of the near rings, characterised by greater differentiation in bond orders, is more marked throughout in the diphenylyl compounds than in their analogues of the phenyl group. In the diphenylylmethyls the outer rings remain aromatic under successive addition of phenyl groups from $x = 1$ to $x = 3$.

The differences in bond order between corresponding bonds of the phenyl molecules or the diphenylyl ones are small, with the exception of the methyl bonds. Together with the trend towards aromatic character of the inner rings this bond changes its order considerably, from a double-bond value to a much smaller single-bond value.

Finally, the graphs (Fig. 4) show that essentially similar results are obtained from calculations by the valence-bond technique as reported by Pullman for the group *A*, *B*, and *C*. While the actual values differ somewhat from our calculated free valences, both methods obtain equivalent sequences of decreasing free valence. Similar curves were published by Coulson and Jacobs (*Dicuss. Faraday Soc.*, 1947, **2**), but the present values include the results for the diphenylyl radicals *D*, *E*, and *F* and have also been corrected for the more recently established value of $N_{max.}$ $(3 + \sqrt{3})$.

(b) *Diradicals.*—Our approach to the investigation of the diradical nature of the meri-quinones falls into three separate aspects which are, nevertheless, closely interconnected. First, we have determined the bond orders of all links in the ground state. Of particular interest are the orders of the ring bonds, for they decide whether the diagrams are of type (I) or (II). The calculated bond-order differences in the central hexagons of *G* and *H* are considerable, and their actual numerical values also warrant a quinonoid structural diagram. As phenyl groups are added to give compounds *J* and *K*, these differences in bond order are smoothed out; all ring orders approach the benzene value, giving a more aromatic character to these rings. The outer phenyl groups of *J* and *K* show only small deviations of bond order from the benzene value and so may be assigned an aromatic bond diagram.

Secondly, we have calculated the probability distributions of the pair of electrons whose orbital energy is small; their energy value justifies the treatment of them as little concerned in bonding, *i.e.*, as almost free electrons. This pair is mostly concentrated at the methyl carbon atoms but on increasing phenylation (transition from *G* to *J* and *H* to *K*) this concentration is reduced to almost half its original value. Substitution of a phenyl group therefore tends to destroy the apparent existence of the free electrons on the end carbons.

A glance at Fig. 6 shows that these almost free electrons also give rise to an alternating distribution going outwards from the methyl carbon atoms in *J* and *K*. This alternation of high and low electron density becomes more pronounced also on passing inwards from the methyl nucleus in changing from *G* to *H*, and from *J* to *K*.

The third and last aspect which has been examined concerns the free valences, in

particular at the methyl carbon atoms. In molecules *G* and *H* the free valence has clearly a maximum value there. This marked favouring with free bonding power of the methyl carbon nuclei is considerably diminished on substitution of a phenyl ring, indeed the free valence does not remain a maximum there for the whole molecule. We conclude that a large free valence in itself need not adequately describe the reactivity of a particular site in the molecule. The reactive centres of the molecules under investigation are known to be the methyl carbon atoms, even for homolytic reactions. A distinguishing feature is that these atoms are throughout surrounded by very low free valence numbers and have also a high non-bonding electron density compared with their nearest neighbours.

A discussion of the radical nature of these compounds has also been given by Schwab and Agliardi (*Ber.*, 1940, *B*, **73**, 95) who have examined Tschitschibabin's hydrocarbon (*K* above) and a number of similar molecules. Magnetic measurements had demonstrated that the molecule as a whole is diamagnetic, *i.e.*, that two independent electron spins do not occur. From their measurements of para-hydrogen conversion, however, the above authors concluded that the compound *K* does show some paramagnetic behaviour. Indeed they find it is as much as 10% diradical in nature.

There certainly exist other factors, however, that influence reactivity, which are not embraced either by the free valence or the non-bonding electron density concept. Indeed a knowledge of the free valence alone may be misleading if used as a guide for predicting reactivity. An example is afforded by the investigation of acenaphthylene due to Coulson and Crawford (*J.*, 1948, 1990). These authors discussed the dimerisation which takes place across the 7 : 8-bond. The large free valence at $C_{(7)}$ and $C_{(8)}$ was considered as theoretical evidence for the greater readiness to form new bonds. A high calculated free valence does, however, also occur at $C_{(3)}$ and $C_{(4)}$, where dimerisation almost certainly does not take place. For if it did, the resulting complex would involve only quinonoid rings, destroying the aromatic nature of the initial naphthalene rings. Thus there is less resonance possible in such an end product which would therefore be of higher energy, *i.e.*, less stable. Free valence alone, they concluded, is an inadequate criterion of reactivity.

Some interest centres on the possibility of a rotation being imposed on a bond that is normally double in these molecules. In the case of compound *K*, a rotation about the central bond leads to two triphenylmethyl radicals. For the latter the odd-electron density and free valence are evaluated in the earlier part of this paper. Now Longuet-Higgins (*loc. cit.*) has shown that if a diamagnetic alternant hydrocarbon is twisted through a right angle from a planar configuration about a C–C bond that is double in all principal resonance structures, the ground state of the twisted configuration is a triplet.

Seel ("F.I.A.T. Reviews of German Science," Vol. I, p. 89) has investigated the possible radical nature of compounds *J* and *K*. He finds that in a planar configuration *K* is not a true diradical; but in the tetrachloro-derivative the molecule has become twisted through a right angle so that two triphenylmethyls in mutually perpendicular configurations arise. The compound then exists as a mesomeric system of a true diradical. This means that no quinonoid valence structures are required in the ground state, and the compound has two independent radical centres. He further demonstrated (*Z. Elektrochem.*, 1948, **52**, 182) that the fact that the molecule behaves in part like a diradical is not due to some form of equilibrium between quinonoid and diradical forms. Rather it is a question of the de-coupling energy of part of the π-electron system required for a change from a quinonoid to a benzenoid structure.

A further theoretical investigation by the M.O. method of this problem has been given by Diatkina and Sirkin (*Acta Physicochem. U.R.S.S.*, 1946, **21**, 23).

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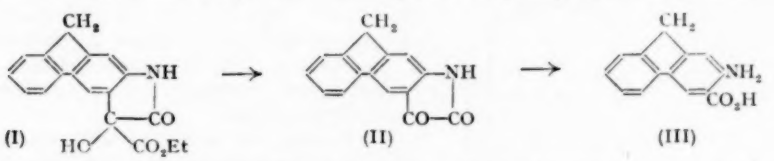
63. *The Ring-closure of Derivatives of 2-Aminofluorene.*

By Neil Campbell and W. H. Stafford.

The product obtained from 2-aminofluorene and ethyl mesoxalate (Neish, *Rec. Trav. chim.*, 1948, **67**, 349) is shown to be ethyl indeno(3′ : 2′-5 : 6)-dioxindole-3-carboxylate (I). Spectroscopic evidence suggests that the product obtained by the Skraup reaction on 2-aminofluorene is indeno-(3′ : 2′-6 : 7)quinoline. The mercuration of fluorene is described and the results of previous workers are criticised. Fluorene-3-carboxylic acid is synthesised.

Exact information of the ring closure of 2-aminofluorene derivatives is lacking. 2-Aminofluorene with ethyl ethoxymethylenemalonate gives a product which was proved by Bremer and Hamilton (*J. Amer. Chem. Soc.*, 1951, **73**, 1844) to be ethyl 1-hydroxyindeno(3′ : 2′-7 : 8)quinoline-2-carboxylate, thereby showing that ring-closure had occurred at position 1 of the fluorene molecule. On the other hand, 2-aminofluorene undergoes the Skraup reaction to give an indenoquinoline (Diels and Staehlin, *Ber.*, 1902, **35**, 3275), and forms with mesoxalic ester an indenoisatin (Martinet reaction) (Neish, *Rec. Trav. chim.*, 1948, **67**, 349) neither of which has been orientated. We have studied both these products in an attempt to determine their chemical constitutions.

Neish's substance is undoubtedly ethyl indeno(3′ : 2′-5 : 6)dioxindole-3-carboxylate (I) since it gives indeno(3′ : 2′-5 : 6)isatin (II) which can be oxidised to 2-aminofluorene-3-carboxylic acid (III). The structure of this acid follows from its deamination to fluorene-3-carboxylic acid, m. p. 231°, which gave a m. p. depression when admixed with



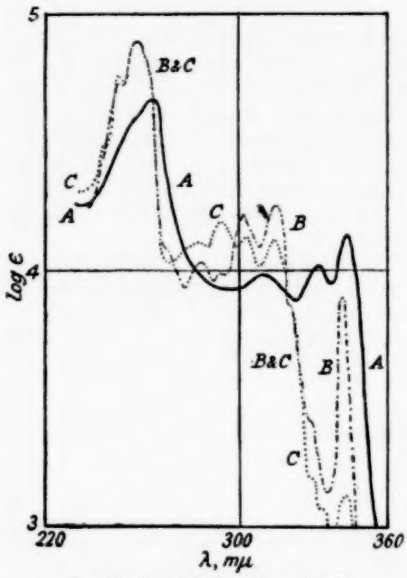
fluorene-1-carboxylic acid, m. p. 245°, but gave no m. p. depression with the 3-acid; on oxidation it yielded fluorenone-3-carboxylic acid, m. p. 300—301°. This value differs considerably from the 285—286° and 283—284° cited respectively by Sieglitz and Schatzkes (*Ber.*, 1921, **54**, 2070) and by Kruber (*Ber.*, 1932, **65**, 1382). We therefore synthesised the keto-acid and purified it *via* the methyl ester. The acid thus obtained had m. p. 304°, and it appears that the acid of the earlier workers was impure. Although it is evident that Kruber would encounter difficulties in purifying the product obtained by oxidising a mixed crystallate of methylfluorenes, it is not so easy to account for the results of Sieglitz and Schatzkes (*loc. cit.*) who oxidised pure 3-methylfluorenone.

To synthesise fluorenone-3-carboxylic acid we first cleaved fluorenone-1-carboxylic acid with alkali. No trace of diphenyl-2 : 3-dicarboxylic acid was found, the only products being diphenyl-2 : 3′-dicarboxylic acid and unchanged fluorenone-1-carboxylic acid; ring closure of the 2 : 3′-diacid by means of sulphuric acid yielded both fluorenone-1- and -3-carboxylic acids. Our results thus differ from those of Mayer and Freitag (*Ber.*, 1921, **54**, 347) who isolated only the 1-acid in 12% yield.

Other attempts to synthesise fluorene- or fluorenone-3-carboxylic acid were unsuccessful. 2-Amino-3-nitrofluorene on deamination gave as the main product a red substance of unknown constitution. The aminonitro-compound was therefore converted into 2-bromo-3-nitrofluorene by a modification of the method of Campbell *et al.* (*J.*, 1940, 446). Reduction gave 3-aminofluorene, but the yield was so poor that further work on these lines was abandoned.

Attempts to prepare 3-bromo-fluorene or -fluorenone from mercurated fluorene were completely unsuccessful. Miller and Bachman (*J. Amer. Chem. Soc.*, 1935, **57**, 2447) claimed by the action of mercuric acetate on fluorene followed by suitable treatment to have prepared two monobromofluorenes, m. p. 90—91° and 165° respectively, the former

of which was stated to be 3-bromofluorene, identical with the product, m. p. 94°, obtained by Clemmensen reduction of 3-bromofluorenone. We have repeated the mercuration of fluorene following closely the directions of the American workers but could find no trace of a monobromofluorene, m. p. 88—94°, and we think it probable that the product with this m. p. was a mixture of fluorene and dibromofluorenes. We isolated a product, m. p. 163°, but found it is a dibromofluorene which on oxidation gives a dibromofluorenone, m. p. 140°. It may be pointed out that the four monobromofluorenones are now known, and the highest m. p. is that of 3-bromofluorenone, *viz.*, 161° (Heilbron and Hey, *J.*, 1938, 1364). This nullifies Miller and Bachman's claim to have oxidised their " monobromofluorene," m. p. 165°, to a bromofluorenone, m. p. 185—187°. From our own work and that of Huntress *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 2845) we conclude that Miller and Bachman's results on the mercuration of fluorene are not reliable.



A. *Product of Skraup synthesis.*
B. 2 : 3-*Benzofluorene.*
C. 1 : 2-*Benzofluorene.*

An attempt was made to orientate the indenoquinoline obtained by the Skraup reaction on 2-aminofluorene (Diels and Staehlin, *loc. cit.*) by comparing its ultra-violet absorption spectrum with those of 1 : 2- and 2 : 3-benzofluorenes (Orchin and Friedel, *J. Amer. Chem. Soc.*, 1949, **71**, 3002). It is apparent from the figure that the spectrum of the indenoquinoline resembles that of 2 : 3- rather than that of 1 : 2-benzoquinoline, thereby suggesting that its structure is indeno(3' : 2'-6 : 7)quinoline. The spectral differences of the benzofluorenes, however, are not sufficient to make the proof final.

Fluorenone-1-carboxylic acid reacts with hydrazine hydrate to give 4-hydroxy-2 : 3-diazafluoranthene which is a useful derivative for the identification and characterisation of the acid. The acid on nitration gives a dinitrofluorenone-1-carboxylic acid of unknown structure.

In studying the effect of hydrazoic acid on fluorene derivatives, we found that sodium azide and sulphuric acid with fluorene yielded chiefly unchanged hydrocarbon and a little 2 : 7-diaminofluorene.

Experimental

Structure of Ethyl Indeno(3' : 2'-5 : 6)*dioxindole-3-carboxylate.*—The indenodioxindole, m. p. 247—249°, was obtained by Neish's method (*loc. cit.*) in 40—50% yields. The substance (0·25 g.) was dissolved in ethanol (5 ml.) and 4N-sodium hydroxide (5 ml.) and treated with perhydrol (2 ml.). The solution was warmed until evolution of oxygen ceased and was then diluted with water (30 ml.) containing sufficient acetic acid to make the solution slightly acid. The precipitated amino-acid was extracted with ether (4 × 25 ml.) and the volume of the dried extract (Na_2SO_4) was reduced to 15 ml. Dry hydrogen chloride was passed through the solutions and the precipitated amino-acid hydrochloride was washed with ether. The hydrochloride in water (5 ml.) gave with saturated sodium acetate solution *2-aminofluorene-3-carboxylic acid* (0·12 g.), plates (from glacial acetic acid), m. p. 256° (Found : C, 74·3; H, 4·3; N, 6·3. $C_{19}H_{11}O_2N$ requires C, 74·7; H, 4·9; N, 6·2%). The amino-acid (0·1 g.) was dissolved in warm 6N-hydrochloric acid (4 ml.). The solution, cooled to 0°, was treated with a slight excess of saturated sodium nitrite solution and the temperature allowed to rise to 10°. Calcium hypophosphite (2 g.) in concentrated hydrochloric acid (4 ml.) and ethanol (4 ml.) was added, and after 2 hours the temperature was raised during ½ hour to 85°. The solution was poured into water (50 ml.) and extracted with ether (2 × 25 ml.). The dried extract (Na_2SO_4) on evaporation gave *fluorene-3-carboxylic acid* (0·042 g.), rhombic prisms, m. p. 231°, after

crystallisation from acetic acid (charcoal) and sublimation (Found : C, 79·2; H, 4·8. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%). The acid (0·05 g.) was oxidised by boiling it in 4N-sodium hydroxide (2 ml.) with potassium permanganate (0·2 g.). Acidification gave fluorenone-3-carboxylic acid (0·02 g.), yellow needles (from acetic acid), m. p. 300—301°, not depressed when mixed with a sample prepared as below.

Indeno(3′ : 2′-5 : 6)isatin was prepared in excellent yield from the carbethoxyindenodioxindole by Neish's method (*loc. cit.*) and was characterised by oxidation to 2-aminofluorene-3-carboxylic acid and by the isolation of the *quinoxaline* derivative by treatment with *o*-phenylenediamine in ethanol. The quinoxaline separated from acetic acid in yellow needles, m. p. >350° (Found : C, 81·6; H, 3·5; N, 13·5. $C_{21}H_{13}N_3$ requires C, 82·1; H, 4·2; N, 13·7%).

Synthesis of Fluorenone-3-carboxylic Acid.—Fluorenone-1-carboxylic acid (10 g.) was added in portions to the emulsion obtained by adding potassium hydroxide (30 g.) to diphenyl ether (125 ml.) and stirring vigorously while the temperature was raised to 200° (bath-temp. 230°). The cooled solution was poured into water (100 ml.), and the flask rinsed with water (50 ml.). Carbon tetrachloride (150 ml.) was added and the aqueous layer which separated was washed with carbon tetrachloride (50 ml.) and on acidification gave a mixture of acids. The acids were extracted for 5 minutes with boiling water (1 l.), and the extract was boiled for 5 minutes with charcoal (2 g.) and filtered. The filtrate on cooling deposited diphenyl-2 : 3′-dicarboxylic acid. The filtrate was used to extract the residue of the first extraction, and the cycle was continued until no further extraction occurred. The residue was fluorenone-1-carboxylic acid, and the acid from the combined filtrates was diphenyl-2 : 3′-dicarboxylic acid (yield variable), m. p. 216—217° (Found : C, 69·6; H, 4·2. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·2%). The methyl ester, prepared from the acid and diazomethane and crystallised from light petroleum (b. p. 40—60°), had m. p. 71—72° (Found : C, 71·3; H, 5·2. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Diphenyl-2 : 3′-dicarboxylic acid (2·5 g.) was warmed in concentrated sulphuric acid (25 ml.) to 140° and kept at this temperature for 1 minute. The solution was poured into water (100 ml.) and boiled. The yellow precipitate was dissolved in boiling ethanol (300 ml.), and the cooled solution deposited a solid (1·3 g.) which was boiled in ethanol (50 ml.) for 10 minutes; one-third to one-half dissolved and the residue was substantially fluorenone-3-carboxylic acid. This acid (0·5 g.) was boiled in methanol (20 ml.) and sulphuric acid (2 ml.) and poured into water. Extraction with ether (4 × 50 ml.), followed by evaporation, gave *methyl fluorenone-3-carboxylate* (0·4 g.), pale yellow needles (from methanol–light petroleum), m. p. 145° (Found : C, 75·4; H, 4·3. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2%). Hydrolysis of the ester by 30% sodium hydroxide solution, followed by acidification, gave the acid, m. p. 304° (Found : C, 74·8; H, 3·6. Calc. for $C_{14}H_8O_3$: C, 75·0; H, 3·5%).

Clemmensen reduction of the acid was unsatisfactory owing to the coating of the zinc with a yellow insoluble gum, but the following modification gave good results. The acid (0·2 g.), dioxan (5 ml.), acetic acid (5 ml.), concentrated hydrochloric acid (2 ml.), and a large excess of amalgamated granulated zinc, previously washed with acid, were boiled with periodic additions of concentrated hydrochloric acid (4 × 1 ml.) until the solution became colourless (*ca.* 2 hours). The solution was decanted from the zinc, concentrated to 3—4 ml., and diluted with water (20 ml.). Fluorene-3-carboxylic acid (0·16 g.) was obtained, having m. p. 230° after crystallisation from acetic acid. Fluorene-1-carboxylic acid was similarly obtained from the corresponding keto-acid.

Synthesis of 3-Aminofluorene.—The mixture of 2-amino-3- and -7-nitrofluorenes (Diels, *Ber.*, 1902, **35**, 328) was partly separated by means of the different basicities of the isomers. The crude 3-compound was chromatographed on alumina (30 g. per g. of crude product), with sulphur-free xylene as developer and eluant. The crimson zone gave an orange-yellow eluate which when concentrated yielded crimson plates of 2-amino-3-nitrofluorene, m. p. 203°, which on crystallisation from acetic acid reverted to the prisms described by Diels (*loc. cit.*). The solution of 2-amino-3-nitrofluorene (3 g.) in boiling glacial acetic acid (30 ml.) was rapidly cooled to give a mass of small crystals which was added to a mixture of sodium nitrite (1·4 g.), concentrated sulphuric acid (10 ml.), and glacial acetic acid (30 ml.), cooled to 10°. The temperature was allowed to rise to 15° and a solution of cuprous bromide (3·5 g.) in concentrated hydrobromic acid (50 ml.) was then rapidly added. The solution was warmed until after 90 minutes the temperature had reached 100°, and the suspension was poured into water (250 ml.). The greenish-yellow solid was filtered off and dried by azeotropic distillation with benzene before being chromatographed on alumina (100 g.). The eluate was collected until it became tinged with red. Removal of the benzene gave 2-bromo-3-nitrofluorene (1·25 g.), pale yellow laths [from light petroleum (b. p. 100—120°) or acetic acid], m. p. 119° (cf. Campbell

et al., loc. cit.). The mother-liquors yielded a further 0·25 g. of material. 2-Bromo-3-nitrofluorene (1·2 g.), stannous chloride (" AnalaR ") (4·5 g.), acetic acid (10 ml.), and concentrated hydrochloric acid (10 ml.) were boiled for 2½ hours, further additions of hydrochloric acid (5 ml.) being made every ½ hour. The solution was poured into an equal volume of cold concentrated hydrochloric acid, whereupon the stannichloride crystallised. This was treated with 20% aqueous sodium hydroxide, and the mixture extracted with ether (2 × 50 ml.). The dried extract (Na_2SO_4) on evaporation gave 3-aminofluorene (0·49 g.), yellow needles, m. p. 149—150° (Found: N, 7·2. Calc. for $C_{13}H_{11}N$: N, 7·6%), from light petroleum (b. p. 80—100°).

Mercuration of Fluorene.—A ground mixture of fluorene (80 g.) and mercuric acetate (160 g.) was fused at 140—145° and the acetic acid produced was condensed and weighed. Miller and Bachman (*loc. cit.*) claim completion of the reaction after 25 minutes, but we found that after 45 minutes only 65% of the required amount of acetic acid was evolved. The mercurichloride was formed by Miller and Bachman's method and was well washed with hot ethanol, acetic acid, and benzene. The pink powder after prolonged drying at 70° weighed 145 g. The mercurichloride (80 g.) was brominated by Miller and Bachman's procedure. Hydrogen sulphide gave a buff-coloured precipitate which was filtered off and extracted several times with hot glacial acetic acid. The combined filtrates were concentrated and yielded crystals, which after crystallisation from light petroleum (b. p. 80—100°), benzene–methanol, and acetic acid gave irregular plates of a *dibromofluorene*, m. p. 163° (Found: Br, 49·2. $C_{13}H_8Br_2$ requires Br, 48·8%). No trace of a lower-melting substance possessing the solubilities reported by Miller and Bachman could be found. The dibromofluorene (0·5 g.) was oxidised in 5 minutes by chromic oxide (" AnalaR; " 0·5 g.) in boiling acetic acid to a *dibromofluorenone* (0·47 g.), elongated prisms (from light petroleum), m. p. 140° (Found: Br, 47·3. $C_{13}H_6OBr_2$ requires Br, 47·3%). It forms a 2 : 4-*dinitrophenylhydrazone*, orange needles (from chlorobenzene), m. p. 340° (Found: N, 10·4. $C_{19}H_{10}O_4N_4Br_2$ requires N, 10·4%). The dibromofluorene with fuming nitric acid in boiling acetic acid gave a *dibromonitrofluorenone*, m. p. 192—193°, after crystallisation from glacial acetic acid (Found: N, 4·1; Br, 44·4. $C_{13}H_7O_2NBr_2$ requires N, 3·8; Br, 43·2%).

Miller and Bachman's second method for preparing fluorene mercurichlorides was also repeated. The product was free from fluorene since it yielded none on steam-distillation. Bromination was effected as before, and the mixture was filtered hot. The filtrate was concentrated in stages, and the first crystalline fraction after being washed with benzene was crystallised first from chlorobenzene and then from nitrobenzene. The product contains both bromine and mercury and is probably a *bromomercuridibromofluorene* (Found: Br, 39·8. $C_{13}H_7Br_3Hg$ requires Br, 39·7%). The filtrate was distilled to remove all the acetic acid and the residue was added to that obtained from the above benzene washings. Steam-distillation gave fluorene, but no bromo-product. The residue from the steam-distillation was distilled up to 250° (bath-temp.)/0·1 mm. The main product was a mixture of dibromofluorenes, principally that of m. p. 163°, and a little 2 : 7-dibromofluorene.

Properties of Fluorenone-1-carboxylic Acid.—The acid (0·20 g.) was boiled with dioxan (5 ml.) and 90% hydrazine hydrate (1 ml.) for 2 hours. 4-*Hydroxy*-2 : 3-*diazafluoranthene* (0·18 g.) separated; crystallised from glacial acetic acid, it had m. p. 267—268° (Found: C, 76·2; H, 3·5. $C_{14}H_8ON_2$ requires C, 76·4; H, 3·6%). Potassium nitrate (1 g.) was added to fluorenone-1-carboxylic acid (1 g.) dissolved in sulphuric acid, and the mixture was warmed on a water-bath to 80° and then poured into water (100 ml.); 2 : 7(?)-*dinitrofluorenone*-1-*carboxylic acid* (0·5 g.) separated and was crystallised from acetic acid; it had m. p. 267° (Found: N, 8·9. $C_{14}H_6O_7N_2$ requires N, 8·9%).

Ultra-violet Absorption Spectrum of Indenoquinoline.—The absorption spectrum was measured by means of a Hilger Barfit medium spectrograph. Absorption maxima occurred at 265 (log ε 4·66), 310 (log ε 3·99), 328 (log ε 4·02), and 342 mμ (log ε 4·14), and minima at 235 (log ε 4·25), 296 (log ε 3·93), 321 (log ε 3·89), and 336 mμ (log ε 3·95).

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64. *Deoxypentose Nucleic Acids. Part III.* Some Effects of Ultrasonic Waves on Deoxypentose Nucleic Acids.*

By S. G. Laland, W. G. Overend, and M. Stacey.

It has been demonstrated that ultrasonic waves disaggregate deoxypentose nucleic acids in dilute aqueous solutions. Changes accompanying this degradation have been investigated and the products have been examined. Results indicate that the products are of relatively high molecular weight. The decrease in viscosity of deoxypentose nucleic acids induced by sonic irradiation has been correlated with changes in the pattern of the titration curves, which can be explained, at least in part, by a decrease in hydrogen bonding. That this is not the entire explanation of the process, however, is indicated by the observed increase in the proportion of secondary phosphate groups. The mechanism of the degradation is discussed. Comment is made on the value of ultrasonic irradiation for rupturing cells during the preparation of nucleic acids from bacterial sources.

Recently we have been interested in isolating, from bacterial sources, various macromolecules and in particular deoxyribonucleic acid (Stacey, *J.*, 1947, 853; Overend, Stacey, Ungar, and Webb, *J. Gen. Microbiol.*, 1951, **5**, 268). In order to disrupt bacterial cells without using chemical reagents some workers (Flosdorf, Kimball, and Chambers, *Proc. Soc. Exp. Biol. N.Y.*, 1939, **41**, 122; Flosdorf and Kimball, *J. Immunol.*, 1940, **39**, 287) have subjected them to ultrasonic vibrations (cf. Zill and van Wagtendonk, *Biochem. Biophys. Acta*, 1951, **6**, 524, for the influence of ultrasonic vibrations on the activity of paramecium). Although this treatment is often effective, we have noted that the deoxypentose nucleic acid obtained from cells disrupted by this procedure gave aqueous solutions of a much lower viscosity than those isolated from similar cells disrupted in a mechanical shaker or a bacterial mill. Consequently it was considered of interest to examine the effect of ultrasonic waves on the chemical and physical properties of deoxypentose nucleic acids.

A further reason for this investigation was to study the nature of hydrogen bonding in deoxypentose nucleic acids. This formed part of an examination of the mode of aggregation of deoxypentose nucleic acids, using the electrometric titration technique (Overend and Peacocke, *Trans. Faraday Soc.*, 1950, **46**, 790; Lee and Peacocke, *J.*, 1951, 3361). Gulland *et al.* (see *Soc. Exp. Biol. Symp.*, 1947, **1**, 1) have proposed that the state of aggregation of deoxypentose nucleic acid is maintained essentially by hydrogen bonds. Evidence for this was drawn from the relation between the marked drop in viscosity of the nucleic acid with its loss of structural character, when acted upon by acid and alkali under very mild conditions, and the effect of these agents in releasing groups for titration in their usual pH ranges. The titration curves of the acid- and the alkali-treated deoxypentose nucleic acid were apparently the same and to account for this it was suggested that the hydrogen bonds linked amino- and enolic hydroxyl groups on the thymine and guanine residues. On this hypothesis, the discrepancy between forward- and back-titration curves of acid- and alkali-treated material should be some criterion of the state of hydrogen bonding of a particular deoxypentose nucleic acid. High-frequency sound waves are known to lower the viscosity and progressively degrade some natural (Flosdorf and Chambers, *J. Amer. Chem. Soc.*, 1933, **55**, 3051; Szent-Gyorgyi, *Nature*, 1933, **131**, 278; Szalay, *Z. physikal. Chem.*, 1933, *A*, **164**, 234; Stacey, *Research*, 1951, **4**, 48; Lockwood, James, and Pautard, *ibid.*, p. 46) and synthetic (Melville and Murray, *Trans. Faraday Soc.*, 1950, **46**, 996) polymers, so that it was thought that electrometric titration of nucleic acids irradiated for varying periods of time with ultrasonic waves would yield valuable information on their state of aggregation and particularly on their mode of hydrogen bonding. A brief preliminary account of the effect of ultrasonic waves on deoxypentose nucleic acids has already been published (Laland, Overend, and Stacey,

* Part II, *J.*, 1951, 2450.

Research, 1950, **3**, 386) and this work has now been amplified and extended (cf. Stern and Goldstein, *J. Polymer Sci.*, 1950, **5**, 687).

The ultrasonic waves (frequency, 213 kc. per sec.) were produced by the well-known method of driving a quartz crystal with the output from a valve oscillator (cf. Melville and Murray, *loc. cit.*). The deoxypentose nucleic acids examined were prepared from calf thymus gland, herring soft roes, and wheat germ. Extensive analytical data concerning these samples will form the subject of a separate communication.

On irradiation, with ultrasonic waves, of 0·2% aqueous solutions of the nucleic acids the viscosity decreased rapidly (see Fig. 1). After irradiation the nucleic acid solutions always showed a pH value less than that of the original solution, contrary to report by

FIG. 1. *Change in viscosity of calf thymus deoxypentose nucleic acid on ultrasonic irradiation.*

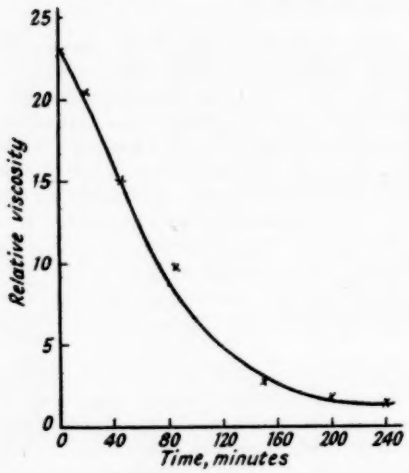
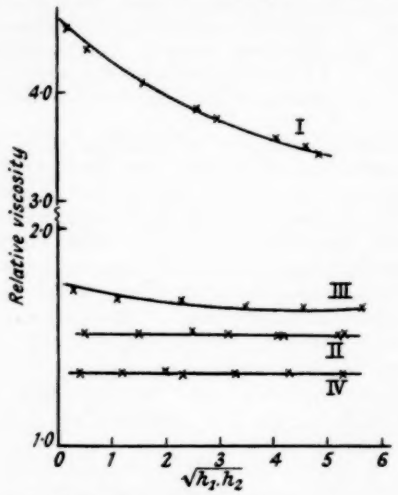


FIG. 2. *Anomalous viscosity of nucleic acids.*

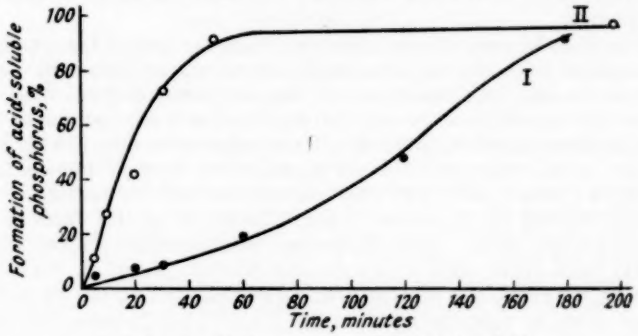


I, *Herring roe nucleic acid.*
II, *Herring roe nucleic acid after ultrasonic irradiation for 95 minutes.*
III, *Wheat germ nucleic acid.*
IV, *Wheat germ nucleic acid after ultrasonic irradiation for 95 minutes.*

Stern and Goldstein (*loc. cit.*) (however, our time of irradiation was more prolonged). The change in pH of our irradiated samples was shown by electrometric titration (Lee and Peacocke, *loc. cit.*) to be correlated with an increase in the number of free primary and secondary phosphoryl groups in the samples. The full significance of this finding will be discussed elsewhere (Overend, Peacocke, and Stacey, forthcoming publication). It is interesting to note that Greenstein, Taylor, and Hollaender (*Cold Spring Harbor Symp.*, 1947, **12**, 237) found no change in titratable acid groups on *X*-irradiation of thymus deoxyribonucleic acid. Furthermore in their work there was no change in acid precipitability; although the ability to be precipitated out of 95% ethanol in the presence of sodium chloride was completely lost in the *X*-irradiated material, ultrasonic-irradiated nucleic acids retained this property. Negligible amounts of ammonia could be detected (method of King, Haslewood, and Delory, *Lancet*, 1937, **1**, 866) in ultrasonic-irradiated solutions of deoxypentose nucleic acid from wheat germ or herring soft roes, but extended irradiation of solutions of calf thymus deoxypentose nucleic acid resulted in some loss, as ammonia, of the nitrogen present (cf. Greenstein *et al.*, *loc. cit.*; Scholes, Stein, and Weiss, *Nature*, 1949, **164**, 711). (Extended irradiation of calf thymus nucleic acid was necessary since it gave more highly viscous solutions than did the other nucleic acids used, and consequently required longer for degradation.) Negligible amounts of inorganic

phosphate were formed and the products from the irradiation were still relatively insoluble in acids. The refractive indices of the native and corresponding irradiated samples in solution were identical, as also were their ultra-violet absorption spectra, thus showing that no groups exhibiting strong absorption were liberated during the irradiation. It is interesting to compare the identity of the absorption spectra of native and sonic-irradiated nucleic acids with the result obtained during the enzymic degradation of deoxypentose nucleic acid. When pancreatic deoxyribonuclease acts on a deoxpentose nucleic acid substrate a fall in viscosity of the substrate occurs, and we find that simultaneously there is a large increase in the intensity of the ultra-violet absorption spectrum (cf. Kunitz, *J. Gen. Physol.*, 1950, **33**, 349). Hence it would seem that the changes in viscosity induced in deoxypentose nucleic acids enzymically and by ultrasonic irradiation are different in character. Solutions of the native and the irradiated materials were dialysed in

FIG. 3. *Action of deoxyribonuclease on herring roe deoxypentose nucleic acid.*



I, *Before irradiation.* II, *After irradiation.*

Cellophane bags at 37° against distilled water. Negligible amounts of material of low molecular weight passed through the membrane, and no free purine or pyrimidine bases were detected. Comparative measurements on diffusion rates with the simple apparatus of Gage (*Trans. Faraday Soc.*, 1948, **44**, 253) on the native and the irradiated samples showed no significant difference, confirming the absence in the irradiated material of polynucleotides of low molecular weight. Hence it seems that although some disaggregation of the deoxypentose nucleic acids is induced by ultrasonic irradiation, the products are still of relatively high molecular weight. Further proof of the disaggregated nature of the irradiation products was provided by an examination of some of their physical properties. Unlike the native deoxypentose nucleic acids which showed structural (anomalous or non-Newtonian) viscosity in the Frampton viscometer (*J. Biol. Chem.*, 1939, **129**, 233), the irradiated products exhibited no anomalous behaviour (see Fig. 2). Since structural viscosity is a reflection of molecular asymmetry and in this case also probably an index of the degree of polymerisation, this result indicates that disaggregation has occurred. Moreover, in the simple apparatus of Edsall and Mehl (*J. Biol. Chem.*, 1940, **133**, 409) the irradiated products did not show the birefringence of flow characteristic of the native material (cf. Greenstein, *Adv. Protein Chem.*, 1944, **1**, 209, and Sparrow and Rosenfeld, *Science*, 1946, **104**, 245, concerning the non-Newtonian viscosity and streaming birefringence of flow of dilute aqueous solutions of deoxypentose nucleic acids). Stern and Goldstein (*loc. cit*) state that the deoxyribose content, as determined colorimetrically by the Dische reaction (*Mikrochem.*, 1930, **8**, 4), was unchanged before and after ultrasonic irradiation of deoxypentose nucleic acids and we have confirmed this. However, after irradiation the nucleic acids gave a somewhat more intense colour when a supersensitive Schiff's reagent (Tobie, *Ind. Eng. Chem. Anal.*, 1942, **14**, 405) was added. This result correlates with earlier evidence (Overend, Stacey, and Webb, *J.*, 1951, 2450) for the existence, in nucleic acids of the deoxypentose type, of a labile polymeric bond which is possibly a glycosidic phosphate linkage (cf. Overend and Stacey, *Nature*, 1949, **163**, 583).

Electrometric titration results supported the view that ultrasonic vibrations disaggregate deoxypentose nucleic acids and indicated that some of the hydrogen bonds are broken (Lee and Peacocke, *loc. cit.*). Enzyme studies on the irradiated material confirmed this. It has been demonstrated that the action of ox-pancreas deoxyribonuclease on deoxypentose nucleic acid results in an initial decrease in viscosity without the formation of acid-soluble polynucleotides (Overend and Webb, *Research*, 1949, **2**, 99; *J.*, 1950, 2746). When the fall in viscosity is complete, onset of formation of acid-soluble polynucleotides commences. When the irradiated samples of deoxypentose nucleic acid were incubated, under identical conditions at pH 7·0, with this enzyme, little further decrease in viscosity occurred and the formation of acid-soluble material commenced immediately (see Fig. 3). It would appear that ultrasonic irradiation disaggregates the nucleic acids to less complex polynucleotides which are susceptible to the nucleotidase action of the enzyme.

The evidence presented shows, that when nucleic acids are isolated from micro-organisms, disruption of the cells by ultrasonic vibrations should be avoided if undegraded samples are required.

It is possible to make some observations on the mechanism of the depolymerisation of deoxypentose nucleic acids by sonic irradiation and to compare this with the *X*-irradiation of these macromolecules. Greenstein *et al.* (*loc. cit.*) showed that, on *X*-irradiation of thymus nucleic acid, the drop in viscosity initiated by the *X*-rays continued after cessation of the irradiation, for a period of about eight hours, whereafter the viscosity levelled off and approached the value consequent on the spontaneous drop of the control specimens. Scholes and Weiss (*Nature*, 1950, **166**, 640) have shown that free radicals, particularly the hydroxyl radical formed by the action of the *X*-radiation on the water of the solutions, was responsible for this effect. Both Butler and his co-workers (*Nature*, 1950, **165**, 714; *J.*, 1950, 3411, 3418, 3421) and Limperos and Mosher (*Amer. J. Roentgenol. Radium Therapy*, 1950, **63**, 681) have also proposed radical mechanisms for the breakdown of deoxypentose nucleic acids in aqueous solutions by *X*-rays and it seems that under suitable conditions hydroxyl radicals and hydrogen atoms are both effective (cf. Lea, "Actions of radiations on living cells," Macmillan Co., New York). Although after the ultrasonic irradiation the viscosity of the solutions of nucleic acid continued to fall very slightly, the change was in no way comparable with the effect observed after *X*-irradiation of similar solutions. Hence it is clear that a radical mechanism is not responsible for the sonic degradation of nucleic acids. Results reported by Melville and Murray (*loc. cit.*) indicated that the degradation by ultrasonic vibrations of dilute solutions of poly(methyl methacrylate) and polystyrene leads to molecules rather than to radicals.

Other possible mechanisms whereby the degradation is induced are (*a*) oxidative fission and (*b*) cavitation. It is also possible that the effect could be thixotropic. At various times evidence for these effects have been examined. Freundlich and Gillings (*Trans. Faraday Soc.*, 1938, **34**, 649), investigating the action of ultrasonic waves on aqueous solutions of gelatin, and toluene solutions of rubber, found that the lowering in viscosity was not permanent. Therefore they concluded that the viscosity change was merely a thixotropic effect and was not due to molecular degradation. These experiments left some doubts as to the results of previous workers who had relied on viscosity measurements alone to prove degradation. The possibility of the viscosity fall being due to a thixotropic effect has been disposed of, however, by Brohult's experiments on the degradation of hæmocyanin (*Nature*, 1937, **140**, 408) and more fully by Schmid and Rommel (*Z. physikal. Chem.*, 1940, *A*, **185**, 98) who worked with chemically better defined synthetic polymers. The latter workers were also able to exclude oxidative fission as the cause of the viscosity fall, a conclusion confirmed by Melville and Murray (*loc. cit.*).

Melville and Murray have shown that degradation can be accomplished without cavitation, but that the breakdown is not so marked as when it is allowed to take place. We have observed that on storage irradiated solutions of nucleic acids do not regain their original viscosities and hence that the effect is not thixotropic, and that irradiation in an atmosphere of nitrogen freed from oxygen causes only a very small difference in the rates of decrease of the viscosity, compared with an irradiation in air. This indicates that oxidative fission can play only a very minor part in the change. It would seem that,

concerning the mechanism of the depolymerisation of nucleic acids by sonic vibrations, Oster's experiments (*J. Gen. Physiol.*, 1947, **31**, 89) on the effect of this treatment on tobacco mosaic virus are of special interest. Electron micrographs lead to the view that the individual virus particles are broken first into halves and then into quarters through the cavitation effect resulting from the sonic vibrations. It is our opinion that sonically irradiated deoxypentose nucleic acids are broken down in similar manner. First, the hydrogen bonds are broken, and then the main polynucleotide chain is ruptured. This leads to the formation of more primary and secondary phosphoryl groups than are found in the native nucleic acid. Stern and Goldstein (*loc. cit.*) have provided sedimentation data which would support this viewpoint. That main valency bonds may be broken through the application of purely mechanical forces to fibre structures is demonstrated by recent experiments by Lundgren and Stein (Abs. of Paper Presented at 114th Meeting of the Amer. Chem. Soc., Portland, Oregon, Sept., 1948).

Experimental

The apparatus used for the generation of the ultrasonic waves consisted of a valve oscillator with two Osram MT 16 valves in parallel, coupled to an X-cut quartz crystal. The applied voltage was about 10 kv and the anode current about 70 milliamp. At maximum output the total energy dissipated by the crystal was *ca.* 100 w, of which about 5% was converted into sound energy. Details of construction of the apparatus and crystal mounting are as described by Melville and Murray (*Trans. Faraday Soc.*, 1950, **46**, 996).

In order to obtain maximum sound energy from the crystal, it is necessary to supply the alternating voltage to the crystal at the same frequency as the fundamental frequency of the crystal. This fundamental frequency is fixed by its dimensions and consequently the oscillator must be tuned to the frequency of the crystal. When the crystal is vibrating under oil, a fountain of oil is thrown up from the surface above the crystal face, and this fountain forms a convenient tuning indicator. Consequently the oscillator was tuned by adjusting the variable condensers in the anode and coupling tuned circuits, until a maximum fountain was obtained.

Samples of Deoxypentose Nucleic Acids Used.—The nucleic acids used were isolated from calf thymus gland, herring soft roes, and wheat germ. The nucleic acid from calf thymus gland was isolated essentially by Mirsky and Pollister's method (*J. Gen. Physiol.*, 1946, **30**, 117). Protein was removed by the Sevag procedure (Sevag, Lackman, and Smolens, *J. Biol. Chem.*, 1938, **124**, 425). The nucleic acid from herring soft roes was isolated in a similar manner, except that it was freed from protein by saturation with sodium chloride (cf. Hammarsten, *Biochem. Z.*, 1924, **144**, 383). Deoxypentose nucleic acid was prepared from wheat germ by the method of Laland, Overend, and Webb (*Acta Chem. Scand.*, 1950, **4**, 885).

Irradiation Procedure.—The solution being irradiated was contained in a glass vessel (capacity, 100 c.c.) which was placed on the surface, and directly above, the fountain of oil. Throughout the irradiation the temperature was kept at 20—22°, by a water cooling system. In each experiment a 0·2% solution (50 c.c.) of the deoxypentose nucleic acid was used.

Viscosity Changes of the Nucleic Acids During Sonic Irradiation.—Viscosity measurements were carried out in an Ostwald viscometer at 25°, on aliquots (4 c.c.) of the nucleic acid solution being irradiated. Initial measurements were usually made 10 minutes after sonic irradiation had commenced. When no appreciable fall in viscosity was noted, the product was isolated by evaporation to dryness in the frozen state. Typical viscosity changes observed for calf thymus deoxypentose nucleic acid, for example, are shown in Fig. 1.

pH *Changes induced by Sonic Irradiation* (cf. Goldstein and Stern, *J. Polymer. Sci.*, 1950, **5**, 687).—Measurements were carried out with a Cambridge Instrument Co. pH meter. Results were :

Source of nucleic acid	Time of irradiation (min.)	pH of solution, initial	pH of solution, final	Change in pH after irradiation
Calf thymus gland	240	5·62	5·00	−0·62
Herring soft roe	95	6·06	5·50	−0·56
Wheat germ	95	5·90	5·46	−0·44

Examination of the Irradiated Samples.—A comparison was made of the properties of the nucleic acids before and after ultrasonic irradiation.

(a) *Precipitation tests* (cf. Greenstein *et al.*, *Cold Spring Harbor Symp.*, 1947, **12**, 237).

Precipitation tests were carried out by adding absolute ethanol (2 vols.) to solutions (0·5%) of the nucleic acids in 1M-sodium chloride. Results were as follows:

Source of nucleic acid	Nature of the precipitate
(i) Thymus gland: before irradiation	Immediate formation of an extremely fibrous ppt.
after irradiation	Slow formation of a flocculent ppt.
(ii) Herring roe: before and after irradiation	Immediate formation of a fibrous ppt.
(iii) Wheat germ: before and after irradiation	Immediate formation of a fibrous ppt.

(b) *Refractive index.* Measurements were carried out with a Hilger refractometer on 0·3% aqueous solutions at 20°:

	Thymus gland	Herring roe	Wheat germ
Before irradiation	1·3359	1·3357	1·3355
After irradiation	1·3359	1·3355	1·3358

(c) *Dialysis.* In a typical procedure an accurately weighed amount of the sample (dried in the frozen state) was dissolved in freshly distilled water (6 c.c.). The solution was placed in a Cellophane dialysis sac which was then suspended in a tube containing water (20 c.c.). The amount of material which had dialysed in 4 hours at 37° was determined from observations on the intensity of the absorption exhibited at 260 mμ by the liquid surrounding the dialysis sac. The following results were obtained:

Sample of nucleic acid	Time of irradiation (min.)	Initial concn. (mg./c.c.)	Dialysis (%)
(1) Thymus gland: before irradiation	0	2·3	0·55
after irradiation	240	2·4	0·90
(2) Herring roe: before irradiation	0	2·3	0·51
after irradiation	95	2·4	0·86
(3) Wheat germ: before irradiation	0	2·4	0·34
after irradiation	95	2·2	1·09

(d) *Diffusion.* The experiments were carried out in the apparatus described by Gage (*Trans. Faraday Soc.*, 1948, **44**, 253) (cf. Overend and Webb, *J.*, 1950, 2746) with filter paper (Whatman, No. 54) as the diffusion membrane. An aqueous solution of the sample (0·0056 g./l.) was introduced into the cell after being preheated at 37° for 30 minutes, and diffusion allowed to proceed for 3 hours at 37° against distilled water (1 l.). The amount of diffusion was determined by measuring the intensity of the ultra-violet absorption of the liquid in the cell. Decreases in the intensity of absorption before and after diffusion were calculated. Only with the nucleic acid isolated from calf thymus gland was there any observable decrease in the intensity of absorption, and this was very small.

(e) *Viscosimetric behaviour.* The viscometer described by Frampton (*J. Biol. Chem.*, 1939, **129**, 233) was used for this investigation. All measurements were carried out at 25° ± 0·05° on 0·1% solutions. The results obtained ($\sqrt{h_1 \cdot h_2}$ being the geometric mean of the hydrostatic pressure in centimetres) are shown in Fig. 2.

(f) *Streaming birefringence of flow.* The streaming birefringence of flow of solutions of the native and irradiated deoxypentosenucleic acids was determined in the apparatus of Edsall and Mehl (*J. Biol. Chem.*, 1940, **133**, 409) (this only gives a rough estimate of the degree of streaming birefringence of flow of a solution). Results obtained were as follows:

Source of nucleic acid	Time of irradiation (min.)	Concn. (%)	Degree of streaming birefringence
Herring roe	0	0·3	+, +
	95	0·3	—
Wheat germ	0	0·3, 0·6, 1·2	−, −, −
	95	0·3	—
Thymus gland	0	0·3	+, +, +
	240	0·3	—

(g) *Ultra-violet absorption spectra.* Measurements of the intensity of the ultra-violet absorption of the various samples in aqueous solution were made with a Unicam spectrophotometer, before and after irradiation, with the following results:

	Nucleic acid from herring roe,		thymus gland,		wheat germ,	
	before	after	before	after	before	after
$P(\varepsilon)_{260\ m\mu}$	7500	7620	7700	7920	7300	7300

($P(\varepsilon)_{260\ m\mu}$ is the molecular extinction coefficient at 260 mμ calculated by using the phosphorus content as the standard of reference. This term was first used by Chargaff and Zamenhof, *J. Biol. Chem.*, **1948**, **173**, 327.)

(h) *Behaviour towards Schiff's reagent.* The sample of nucleic acid (*ca.* 2 mg.) was dissolved in freshly distilled water (8 c.c.) contained in a thoroughly cleaned boiling-tube. Supersensitive Schiff's reagent (Tobie, *Ind. Eng. Chem. Anal.*, 1942, **14**, 405) (1 c.c.) was added and then the tubes were securely sealed. After 90 and 210 minutes the intensity of the colour developed was measured with the Hilger (Spekker) photoelectric absorptiometer and Ilford filter No. 605 ($\lambda = 5500$ Å). All measurements were made under controlled conditions of temperature. Results, before and after irradiation, were as follows :

	Nucleic acid from thymus gland,		herring roe,		wheat germ,	
	before	after 240 min.	before	after 95 min.	before	after 95 min.
ε_p at 550 mμ after 90 min. ...	110	142	96	130	108	140
ε_p at 550 mμ after 210 min. ...	275	280	250	275	275	300

($\varepsilon_p = RA/cd$ when A = atomic weight of phosphorus, R = instrument reading, c = g. of phosphorus per l. of nucleic acid solution, and d is the thickness of the cell in cm.)

(i) *Action of deoxyribonuclease.* (1) Viscometric changes. The viscometric changes were observed which resulted from the action of a 0·0018% aqueous solution of deoxyribonuclease (prepared according to McCarty's method, *J. Gen. Physiol.*, 1946, **29**, 123) on a digest consisting of a solution of the deoxyribonucleic acid (before and after irradiation) (0·13%) which was 0·18M. with respect to both magnesium sulphate and veronal buffer (pH 6·92). An Ostwald viscometer was used and all the observations were made at 37° on aliquots of 4 c.c. Typical changes in viscosity observed are shown in Fig. 3.

(2) Formation of acid-soluble polynucleotides. The substrate and enzyme preparations used were identical with those already described, except for the experiments with wheat germ nucleic acid. In this case the concentrations of the nucleic acid and enzyme were 0·11% and 0·0004% respectively and the digest was 0·022M. with respect to magnesium sulphate and the veronal buffer. At intervals, aliquots (2 c.c.) were withdrawn and acid-insoluble material was precipitated by addition of 5N-hydrochloric acid (0·3 c.c.). The precipitate was removed at the centrifuge, and the phosphorus content of the supernatant liquid was determined by Allen's colorimetric method (*Biochem. J.*, 1940, **34**, 858). The following results were obtained :

Herring roe nucleic acid

Before irradiation :								
Time (min.)	5	20	30	40	60	120	180	225
Formation of acid-sol. P (% of total P)	5·5	7·9	7·9	18·8	18·8	48·0	92·0	100·0
After irradiation :								
Time (min.)	5	10	20	30	50	200	260	
Formation of acid-sol. P (% of total P)	10·6	27·0	41·5	73·0	91·0	96·0	100·0	

Thymus gland nucleic acid

Before irradiation :									
Time (min.)	20	40	60	80	116	146	176	305	380
Formation of acid-sol. P (% of total P)	5·5	9·5	10·0	9·5	15·2	24·0	29·5	71·0	96·0
After irradiation :									
Time (min.)	10	20	40	60	90	120	150		
Formation of acid-sol. P (% of total P)	9·0	9·3	20·5	30·0	41·5	64·5	83·0		

Wheat germ nucleic acid

Before irradiation :								
Time (min.)	5	15	30	50	70	95		
Formation of acid-sol. P (% of total P)	45	61·5	82	87	91	96		
After irradiation :								
Time (min.)	5	15	30	50				
Formation of acid-sol. P (% of total P)	58	70	85	98				

Estimation of the Inorganic and Acid-soluble Phosphorus formed during Irradiation.—A solution of the irradiated nucleic acid sample in distilled water (5 c.c.; 2 mg. of nucleic acid per c.c.) was placed in a centrifuge tube and precipitated by the addition of 5N-hydrochloric acid (0·5 c.c.). The precipitate was removed at the centrifuge and analyses were carried out on aliquots (2 c.c.) of the supernatant liquid for inorganic phosphate and organic-bound acid-soluble phosphorus compounds. In addition the total phosphorus content of the original nucleic acid solution was determined.

Source of irradiated nucleic acid	Phosphorus present as inorg. phosphate (% of total phosphorus)	Acid-soluble phosphorus (% of total phosphorus)
Calf thymus gland	1·0	2·0
Herring soft roes	1·0	2·0
Wheat germ	1·0	4·0

Changes occurring during and after irradiation.—(a) *Liberation of ammonia* (cf. King, Haslewood, and Delory, *Lancet*, **1937**, **1**, 866). A solution of nucleic acid (2 c.c.), irradiated as described, was diluted with distilled water (5 c.c.) and standard Nessler's reagent (1 c.c.) was added. The intensity of the colour developed after 5 minutes was measured in the Spekker photoelectric absorptiometer with Ilford filter No. 602. Calibration of the intrument with a standard solution of ammonia gave a means of measuring the ammonia content of the nucleic acid solution. Results were as follows :

Source of nucleic acid	Time of irradiation (min.)	Nitrogen present as ammonia (% of total N content of the nucleic acid solution)
Herring soft roes	90	<0·6
Wheat germ	110	<0·6
Calf thymus gland	240	1·25

It was shown that by use of this method it was possible to detect 0·0025 mg. of ammonia.

In control experiments it was possible to demonstrate that any ammonia formed during irradiation was not evolved : a 0·2% solution of herring roe deoxypentose nucleic acid containing added ammonia (0·0144 mg. of nitrogen per c.c.) was submitted to ultrasonic irradiation at 20° and pH 5·5 for 120 minutes; the ammonia in the solution was estimated by the above method before and after irradiation; there was no appreciable change.

(b) *Change in viscosity after irradiation.* A 0·2% solution of herring roe deoxypentose nucleic acid was submitted to ultrasonic irradiation for 20 minutes. The viscosity of the solution was determined 3 minutes after the cessation of the irradiation, and thereafter the solution was maintained at 25° and its viscosity measured at intervals. A similar experiment was carried out with calf thymus gland nucleic acid, except that the initial irradiation treatment was maintained for 60 minutes. Results were as follows :

Herring roe nucleic acid						*Calf thymus nucleic acid*		
Time (min.) ...	3	9	90	255	960	Time (min.)	5	960
$\eta_{rel.\ H_2O}$	2·14	2·11	2·08	2·08	2·07	$\eta_{rel.\ H_2O}$	13·6	12·1

(c) *Ultrasonic irradiation in an atmosphere of nitrogen.* A solution of calf thymus deoxypentose nucleic acid (0·07%; $\eta_{rel.}$ 3·65) (20 c.c.) was placed in a closed glass vessel, and nitrogen (freed from oxygen by passage over a heated copper spiral) was bubbled through the solution for 1 hour. The vessel was then sealed and the solution irradiated with ultrasonic vibrations for 35 minutes. After this period the relative viscosity of the solution was 1·62, whereas the control solution irradiated in the presence of oxygen had a relative viscosity of 1·47 (cf. Melville and Murray, *loc. cit.*, for an account of the slight variations of viscosity which occur in a series of experiments under apparently identical conditions).

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65. *Condensation of o-Acetoxybenzaldehyde with Malonic Acid and Ethyl Malonate.*

By P. M. Bhargava and S. Husain Zaheer.

Condensation of *o*-acetoxybenzaldehyde with malonic acid or ethyl malonate, in presence of pyridine, involves partial ring-closure to coumarin derivatives. Some aryl esters of coumarin-3-carboxylic acid have been shown to have no insecticidal action on house-flies.

The pyridine-catalysed condensation of salicylaldehyde with malonic acid or ethyl malonate gives respectively coumarin-3-carboxylic acid and its ethyl ester (Knoevenagel, *Ber.*, 1898, **31**, 2596; Kurien, Pandya, and Surange, *J. Indian Chem. Soc.*, 1934, **11**, 823; Khan, Kurien, and Pandya, *Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 440; Knoevenagel and Hoffmann, *Ber.*, 1898, **31**, 2593; Kurien, Peter, and Pandya, *Proc. Indian Acad. Sci.*, 1935, **1**, *A*, 775; Horning, Horning, and Dimmit, *Org. Synth.*, 1948, **28**, 24). We have now found that replacement of this aldehyde by its acetyl derivative leads, with malonic acid to coumarin-3-carboxylic acid (38·7%) and 2-acetoxycinnamic acid (28%), and with ethyl malonate to ethyl coumarin-3-carboxylate (45·1%) and ethyl salicylidenemalonate (37%). It is interesting that a molecule of ethyl alcohol is not eliminated from the malonic ester during the condensation.

Ethyl salicylidenemalonate yielded coumarin-3-carboxylic acid on hydrolysis with acid, and with concentrated aqueous ammonia, gave the ester-amide which is also hydrolysed to coumarin-3-carboxylic acid by mineral acid. Ethyl salicylidenemalonate with acetyl chloride and pyridine, or with acetic anhydride and anhydrous sodium acetate, gave ethyl coumarin-3-carboxylate. These reactions prove the structure assigned to the salicylidenemalonate.

During this work, some aryl esters of coumarin-3-carboxylic acid were prepared. These had no insecticidal action on house-flies.

Experimental

o-Acetoxybenzaldehyde.—This was prepared by Perkin's method (*Annalen*, 1868, **148**, 203) in 75% yield and had b. p. 110—112°/1 mm., m. p. 37°.

Condensation of o-Acetoxybenzaldehyde with Malonic Acid.—*o*-Acetoxybenzaldehyde (20·5 g., 0·125 mol.), malonic acid (13 g., 0·125 mol.) and dry pyridine (1·6 g., 0·02 mol.) were heated at 100° for 4 hours and then left overnight. The product was treated with 2% hydrochloric acid (80 c.c.); the oil that separated solidified at 0° to a colourless crystalline mass which was filtered off and extracted with ether. Coumarin-3-carboxylic acid (9·2 g., 38·7%) was insoluble; recrystallised from hot water, it had m. p. 189° alone or mixed with an authentic sample (Kurien, Pandya, and Surange, *loc. cit.*). The ethereal extract, after drying and evaporation of the ether, yielded 2-acetoxycinnamic acid (7·2 g., 28%) which was purified by extraction with 8% sodium carbonate solution, precipitation with hydrochloric acid, and recrystallisation twice from hot water; it had m. p. 152—153° and with 10% potassium hydroxide yielded 2-hydroxycinnamic acid, m. p. 210—211°, in quantitative yield.

Coumarin-3-carboxylic acid dissolves only slowly in cold dilute aqueous sodium carbonate, sodium hydrogen carbonate, or sodium hydroxide.

Coumarin-3-carboxylic Acid Derivatives.—Thionyl chloride (98·7 g., 3 mols.) was added dropwise, with ice-cooling, to coumarin-3-carboxylic acid (52·5 g.), and the mixture refluxed for 2 hours. Next morning the chloride (53 g., 92%) was filtered off and washed with dry ether (100—125 c.c.); though slightly coloured, the product was almost pure, m. p. 146—147°. Recrystallisation from dry acetone gave colourless crystals, m. p. 147—148° (cf. Boehm and Schumann, *Arch. Pharm.*, 1933, **271**, 490). The chloride is not affected appreciably by exposure to air for 24 hours, though completely hydrolysed by boiling water in 10 minutes.

To the crude chloride (from 0·6 g. of acid) in acetone (10 c.c.), freshly-distilled aniline (1 c.c.) was added dropwise, with ice-cooling, followed by 10% sodium hydroxide (30 c.c.). The mixture was shaken for 10 minutes, left in a refrigerator for some time, and then treated

with ether. Fine yellow crystals of the pure anilide separated (0·8 g.), which were filtered off and washed with ether; it had m. p. 249—250° (cf. Merck, *Chem. Zent.*, 1906, II, 724).

Aqueous ammonia (10 c.c.) was added dropwise to crude coumarin-3-carboxyl chloride (from 0·6 g. of acid) at 0°. After an hour, the amide formed in quantitative yield was filtered off, washed with water, and recrystallised from methyl–ethyl alcohol (1 : 1), yielding flaky needles, m. p. 267—268° (cf. Merck, *loc. cit.*).

Coumarin-3-carboxyl chloride and the appropriate phenol (equimol. quantities) were heated at 100° for 2—6 hours. The mixture darkened, solidifying later in some cases. It was left overnight, then treated with water (75—125 c.c.), and again left overnight in a refrigerator. The solid product was either filtered off or washed by decantation. The crude ester thus obtained was recrystallised from hot alochol, except in the case of the *p*-nitrophenyl ester which was sparingly soluble in alcohol, benzene, toluene, xylene, acetone, ethyl acetate, or acetic acid. This ester was purified by leaving the finely powdered crude product covered with sodium hydroxide for 48 hours, filtering, and washing the residue with water and then with a little alcohol; the whole process was subsequently repeated.

The *esters* prepared are described in the Table.

				Found, %		Required, %	
Ester	Form	M. p.	Formula	C	H	C	H
Phenyl	Plates	156°	$C_{16}H_{10}O_4$	72·0	3·9	72·2	3·8
o-Tolyl	Needles	131—132	$C_{17}H_{12}O_4$	73·1	4·6	72·9	4·3
m-Tolyl	—	164—165	$C_{17}H_{12}O_4$	72·9	4·3		
m-Methoxyphenyl	Needles	121—122	$C_{17}H_{12}O_5$	68·7	4·1	68·95	4·05
p-Methoxyphenyl	—	167—168	$C_{17}H_{12}O_5$	68·8	4·1		
p-Ethoxyphenyl	Needles	169	$C_{18}H_{14}O_5$	69·6	4·2	69·7	4·5
p-Nitrophenyl	—	274—276	$C_{16}H_9O_6N$ *	61·3	2·9	61·7	2·9

* Found: N, 4·3. Required: N, 4·5%.

Condensation of o-*Acetoxybenzaldehyde with Ethyl Malonate.*—o-Acetoxybenzaldehyde (24·6 g., 0·15 mol.), ethyl malonate (24 g., 0·15 mol.), and pyridine (2·37 g., 0·03 mol.) were heated in an oil-bath at 105—110° for 15 hours. After cooling, the product was treated with water (70 c.c.) and 18% hydrochloric acid (15 c.c.), then shaken with ether (50 c.c.), after which it was left in a refrigerator overnight. Ethyl coumarin-3-carboxylate which crystallised was filtered off and recrystallised from hot alcohol; it had m. p. 93—94° (4·71 g., 45%). With 10% potassium hydroxide solution (3—4 hours), it yielded coumarin-3-carboxylic acid, m. p. 189°, in quantitative yield. The ester was converted quantitatively into coumarin-3-carboxyamide, m. p. 267—268°, by keeping it in aqueous ammonia (5 c.c.) at room temperature for 48 hours. The ethereal layer from the filtrate obtained after the separation of ethyl coumarin-3-carboxylate, was washed with water and dried (Na_2SO_4). After evaporation, the residue was distilled in a vacuum, giving *ethyl salicylidenemalonate* as a sweet-smelling liquid (13·3 g., 33·6%) which was purified by redistillation (b. p. 74—76°/1·2 mm.) (Found: C, 63·05; H, 6·3. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). During the first distillation, a small residue (*ca.* 2 g.) proved to be ethyl coumarin-3-carboxylate. Ethyl salicylidenemalonate gives a deep violet colour with 1% ferric chloride, decolorises acidic potassium permanganate and bromine water, and is very slightly soluble in water, the aqueous extract being faintly acid to litmus. It dissolves in dilute aqueous sodium hydroxide to yield a deep yellow solution from which it is reprecipitated unchanged by dilute hydrochloric acid.

Hydrolysis of Ethyl Salicylidenemalonate.—The ester (4 g.) was refluxed with 50% sulphuric acid (50 c.c.) for 3 hours and then left in a refrigerator overnight. The coumarin-3-carboxylic acid (2·5 g., 83%) was filtered off and recrystallised, and had m. p. 189° alone or mixed with an authentic sample.

Hydrolysis of the ester (1·5 g.) could also be effected with acetic (6 c.c.) and 10% sulphuric (15 c.c.) acids; the yield of coumarin-3-carboxylic acid in this case was, however, much lower (0·4 g., 30%).

Ethyl α-Carbamyl-2-hydroxycinnamate.—Ethyl salicylidenemalonate (7 g.) was treated propwise with excess of cold aqueous ammonia (20 c.c.). A brisk reaction took place accompanied by profuse separation of a yellow solid. The mixture was left for 0·5 hour and then filtered. The *amide-ester* (5 g., 80·2%) was washed well with water and recrystallised from hot alcohol, to yield yellow crystals, m. p. 136—137° (Found: C, 61·8; H, 5·8; N, 5·75. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%). The product gives ammonia when heated with dilute sodium hydroxide solution, in which it is soluble in the cold, being reprecipitated unchanged by dilute hydrochloric acid. It slowly gives a deep violet colour with ferric chloride.

When the amide (0·4 g.) was heated with 50% sulphuric acid (9 c.c.) for 15 minutes, it dissolved. On cooling in ice, coumarin-3-carboxylic acid, m. p. 189° (after recrystallisation), separated out in quantitative yield.

Attempts to Acetylate Ethyl Salicylidenemalonate.—(*a*) Acetyl chloride (9 g.) was added dropwise, with stirring, to an ice-cooled solution of the hydroxy-compound (10 g.) in pyridine (6 c.c.). After the brisk reaction had subsided, the mixture was set aside at room temperature for a day, then poured into dilute hydrochloric acid containing lumps of ice, and left in a refrigerator overnight. The separating ethyl coumarin-3-carboxylate (5 g., 60·5%) was filtered off and recrystallised; it had m. p. (and mixed m. p. with an authentic sample) 93—94°.

(*b*) Ethyl salicylidenemalonate (15 g.), acetic anhydride (12 g.), and anhydrous sodium acetate (6·9 g.) were refluxed for 4 hours. After cooling, addition of ice-water (125 c.c.) precipitated an oil which solidified at 0° overnight. Ethyl coumarin-3-carboxylate thus obtained (10·5 g., 84·8%) was filtered off and recrystallised; it had m. p. (and mixed m. p.) 93—94°.

(*c*) The hydroxy-compound was not acetylated by refluxing it with 3 times the required amount of acetyl chloride for 2 hours, the original substance being recovered unchanged.

Toxicity Tests with Esters of Coumarin-3-carboxylic Acid.—The esters (see table) were tested on adult house-flies, at a concentration of 2·5% in benzene, by means of a modified Potter's spraying apparatus (*Ann. Appl. Biol.*, 1941, **28**, 142); three were also tested at a concentration of 5%. Twenty flies were used and 2 c.c. of the benzene solution sprayed in each experiment, which was conducted in duplicate. None of the esters exhibited lethal activity, except *p*-methoxyphenyl coumarin-3-carboxylate where a 15% mortality was observed against none in the control.

The toxicity tests were carried out by Mr. M. B. Naidu, to whom we express our grateful thanks. The work was made possible by the award to one of us (P. M. B.) of a research scholarship by the Board of Scientific and Industrial Research, Hyderabad-Deccan, and later of a fellowship from the National Institute of Sciences of India, for which he wishes to record his gratitude.

CENTRAL LABORATORIES FOR SCIENTIFIC AND INDUSTRIAL RESEARCH,
HYDERABAD-DECCAN, INDIA. [*Received, August 30th*, 1951.]

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66. *The Structure of Sterculic Acid.*

By J. R. NUNN.

Sterculic acid, the main constituent of the kernel oil of *Sterculia fœtida*, has been isolated in a pure state by means of its urea complex, and evidence is presented for its being ω-(2-*n*-octyl*cyclo*prop-1-enyl)octanoic acid. Sterculyl alcohol has been prepared.

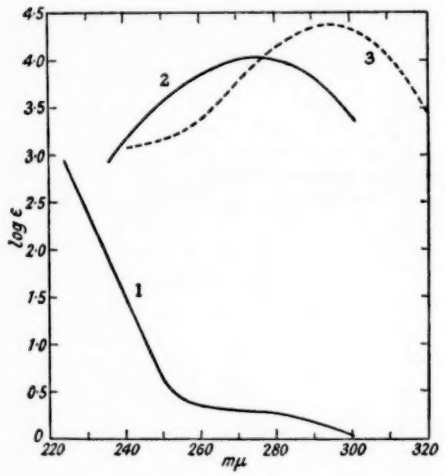
THE kernels of the seeds of *Sterculia fœtida* give, on extraction with 2-methylpentane, a pale yellow oil which undergoes rapid thermal polymerization at 250° and even to some extent below this temperature. Previous attempts to isolate the acid responsible for this property failed owing to the ease with which the acid and its esters polymerize.

Steger and van Loon (*Fette u. Seifen*, 1943, **50**, 305), working on the mixed fatty acids, concluded that the acid responsible for this property was a saturated hydroxy-acid, probably $C_{18}H_{34}O_3$. Hilditch, Meara, and Zaky (*J. Soc. Chem. Ind.*, 1941, **60**, 198T), distilled the hydrogenated mixed methyl esters and deduced that the original mixed acids contained 72% of a doubly unsaturated acid, $C_{19}H_{34}O_2$. By degradative experiments on the mixed methyl esters, they concluded that it was 12-methyloctadeca-9 : 11-dienoic acid. However, the ultra-violet absorption spectrum of the oil gave no band characteristic of two conjugated double bonds (Braude, *Ann. Reports*, 1945, **42**, 105), so that this structure is very unlikely.

The acids were isolated by saponification of the oil in the cold and then separated by fractional crystallisation of their urea complexes from methanol (cf. Schlenk and Holman, *J. Amer. Chem. Soc.*, 1950, **72**, 500). The saturated acids appeared in the first fractions and the main acid component, for which the name sterculic acid is proposed, in the last fractions. Further purification by low-temperature crystallisation from acetone yielded pure sterculic acid of m. p. 18·2°. It had the formula $C_{19}H_{34}O_2$ and polymerized fairly rapidly at room temperature, and even slowly at 0°, the equivalent weight increasing with time. Partly polymerized material could be saponified to yield an acid having nearly the same equivalent weight as the original material, but this acid has not yet been

Solvent	Max., Å	ε	Concn., mole/l.
Ethanol	2750	10 500	0·0001
,, ...	2760	15 900	0·0000114
Ethanolic NaOH	2955	22 800	0·0001

investigated. Sterculic acid does not react with pyridine–acetic anhydride and contains one active hydrogen atom per mole (lithium aluminium hydride method; Hochstein, *J. Amer. Chem. Soc.*, 1949, **71**, 305). It is optically inactive and its absorption spectrum



1, *Sterculic acid.* 2, 9 : 11-*Diketononadecanoic acid* (0·0001 *mole/l.*) *in ethanol.* 3, 9 : 11-*Diketononadecanoic acid* (0·0001 *mole/l.*) *in ethanolic sodium hydroxide.*

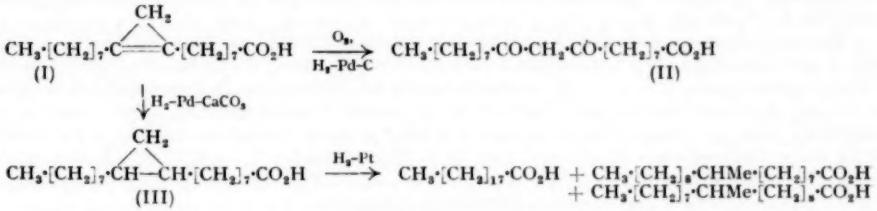
(see figure) indicates the absence of conjugated unsaturation. On hydrogenation in ethanol in the presence of palladised calcium carbonate it absorbed hydrogen equivalent to one double bond. The dihydrosterculic acid so obtained gave no colour with tetranitromethane but, in presence of Adams's platinum catalyst, absorbed a further mole of hydrogen. The fully hydrogenated product melted over a wide range (63—66·5° after one crystallisation), but elementary analysis was in very good agreement with the formula $C_{19}H_{38}O_2$. The fully hydrogenated product is probably a mixture of *n*-nonadecanoic acid (m. p. 68·6°) and two methyl-substituted octadecanoic acids.

Oxidation of sterculic acid with potassium permanganate in acetone gave, as main products, pelargonic and azelaic acids. When sterculic acid was ozonised in acetic acid and the ozonide decomposed with acetic acid–hydrogen peroxide, pelargonic and azelaic acids only were obtained, in good yield. Ozonolysis in ethyl acetate at low temperature and reduction of the ozonide with hydrogen in the presence of palladised charcoal gave a little formaldehyde (<1/5 mol.) but most of the material had been converted into an acid, $C_{19}H_{34}O_4$, m. p. 57·5—58·3°. An accurate equivalent weight determination was not possible because of fading of the end-point during titration. On oxidation with hydrogen peroxide in acetic acid, the compound $C_{19}H_{34}O_4$ gave pelargonic and azelaic acids as the only fission products, in good yields; it gave a deep red colour with ferric

chloride and its absorption spectrum was characteristic of 1 : 3-diones (cf. Bastron, Davis, and Butz, *J. Org. Chem.*, 1943, **8**, 515); the position and intensity of the maximum were dependent on the concentration and on pH (see table and figure); this behaviour is in agreement with the tautomeric nature of 1 : 3-diones and hence the substance $C_{19}H_{34}O_4$ must be 9 : 11-diketononadecanoic acid (II).

This conclusion, together with the other evidence presented above, is consistent with the structure, ω-(2-*n*-octyl*cyclo*prop-1-enyl)octanoic acid (I), for sterculic acid.

The *cyclo*propene structure for sterculic acid explains the stepwise hydrogenation to give, first, (III), having a *cyclo*propane ring capable of being ruptured by hydrogen and yet resistant to oxidation. Hydrogenation of (III) can proceed so as to give three products which would account for the melting point range observed in the fully hydrogenated product. Hoffmann and Lucas (*J. Amer. Chem. Soc.*, 1950, **72**, 4328) have isolated a C_{19} saturated acid from *Lactobacillus arabinosus*, which is resistant to oxidation and yet is hydrogenated to give three products formulated as *n*-nonadecanoic acid and a mixture



of two methyloctadecanoic acids. They have proposed a *cyclo*propane structure for the acid, strong supporting evidence being given by an absorption maximum at 9·8 μ (cf. Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482).*

The isolation of a trace of formaldehyde on ozonolysis is the only evidence which does not fit the structure (I) for sterculic acid easily. It seems remotely possible that, if a trace of water were present, formaldehyde may have arisen by hydrolytic fission of 9 : 11-diketononadecanoic acid (II), but pelargonaldehyde and azelaic semialdehyde were not detected. On the other hand, it may have arisen as a result of the peculiar nature of the ozonide.

The double bond in the *cyclo*propene ring would be highly reactive and it seems likely that sterculic acid polymerizes by reaction of the carboxyl group with the double bond. The polymerization of the oil obviously involves a different mechanism.

Sterculyl alcohol, made by reduction of the acid with lithium aluminium hydride, underwent the same stepwise hydrogenation as sterculic acid itself, showing that the *cyclo*propene ring was intact.

Experimental

M. p.s are corrected.

Extraction and Saponification of the Oil.—On the advice of the Department of Botany and Plant Pathology, Pretoria, seeds for this investigation were obtained from the Bosbouwproefstation, Department van Landbouw, Buitenzorg, Indonesië, Java, and from the Bureau of Forestry, Manila, Philippine Islands. The hard shells of the seeds were removed and the kernels (ca. 48% of the seed) pulverized to a fine meal. Extraction (Soxhlet) with 2-methylpentane yielded a pale yellow oil (51%). However, since a yield of 45% of oil was obtained by stirring the crushed kernels with four changes of warm 2-methylpentane, this procedure was adopted for large-scale preparations.

Saponification was effected by dissolving the oil in a cold concentrated solution of alcoholic potassium hydroxide and leaving the whole overnight. The acids (90% of the oil) were liberated with sulphuric acid and isolated in ether. After the ether had been evaporated from the dried (Na_2SO_4) extract, the acids were dried in a vacuum at room temperature.

* *Added in Proof.*—Dihydrosterculic acid shows an absorption maximum at 9·85 μ.

Fractionation of the Acids.—The initial urea complex was formed by adding the mixed acids (121 g.) to a solution of urea (121 g.) in methanol (363 c.c.) at the b. p. Complex no. 1 separated on cooling. All subsequent complexes were formed by adding the requisite amount of finely divided urea to the filtrate from the preceding complex. The mixture was warmed to dissolve the urea and then cooled again to allow the new crop of complex to crystallise. The complexes were decomposed by shaking them with water–ether, a little sulphuric acid being added to prevent emulsion formation. The progress of fractionation is shown in the table.

Urea added,	Complex,		Urea added,	Complex,	
g.	g.	no.	g.	g.	no.
121	101	1	60	82	4
60	77	2	80	53	5
30	21	3			

The filtrate from complex no. 5, when concentrated to one-third of its volume, deposited complex no. 6 (47 g.). The filtrate therefrom, concentrated to half its volume, deposited complex no. 7 (24 g.).

Recovery from complex No. 1 gave mainly a mixture (29 g.) of saturated acids. Complex No. 2 gave a mixture (20 g.) of saturated and unsaturated acids. Complex No. 3 gave a mixture of unsaturated acids (5·5 g.). The acids (total, 50 g.) obtained on decomposition of complexes 4—7 and the final filtrate were crystallised separately from acetone at −50°, and the pure materials dried at 1 mm., with a nitrogen bubbler, at room temperature. The acids obtained from these fractions were all *sterculic acid*, m. p. 18·2° (Found: C, 77·5, 77·6; H, 11·9, 11·9%; active H, 1·03 atoms. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·6%; active H, 1·0 atom). The acid gave a yellow colour with tetranitromethane in chloroform.

Sterculic acid polymerized too rapidly, even at room temperature, for its equivalent weight to be determined by titration: 2 hours after its preparation a sample gave the value 308 ($C_{19}H_{34}O_2$ requires equiv., 294·5). The rate of polymerization at 96° in a nitrogen atmosphere was determined by titrating samples at intervals:

Time (min.)	0	10	20	40	60	80	170	230
Equiv.	(294)	373	414	526	700	814	1220	1460

The solubility in ethanol decreased with increasing molecular weight, but the material was soluble in benzene.

Partly polymerized material could be saponified to yield an acid of lower equivalent weight. Thus material of equivalent weight 424 by direct titration gave an equivalent weight of 300 by saponification. The resulting acid could not be induced to crystallise.

Hydrogenation of Sterculic Acid.—Sterculic acid (9·41 mg.) in ethanol in the presence of palladised calcium carbonate absorbed 0·784 c.c. of hydrogen (N.T.P.) ($C_{19}H_{34}O_2$ requires 0·715 c.c. for one double bond). After hydrogenation of 1 g. of acid, the product was isolated by evaporation of the ethanol in a vacuum and then recrystallised from acetone at −10°; it had m. p., 38·8—39·8° (Found: C, 77·1; H, 12·2%; equiv., 298. $C_{19}H_{36}O_2$ requires C, 77·0; H, 12·2%; equiv., 296·5). It gave no colour with tetranitromethane in chloroform and was not oxidised by potassium permanganate in boiling acetone. In glacial acetic acid and in the presence of Adams's platinum catalyst, *dihydrosterculic acid* (24·11 mg.) absorbed 1·65 c.c. (0·95 mol.) of hydrogen (N.T.P.).

Sterculic acid [(*a*) 23·13 mg.; (*b*) 22·19 mg.] in glacial acetic acid in the presence of Adams's platinum catalyst absorbed (*a*) 3·38 c.c. (1·92 mol.), (*b*) 3·22 c.c. (1·91 mol.) of hydrogen (N.T.P.). Whereas the hydrogenation with palladised calcium carbonate was complete in a few minutes, hydrogenation with Adams's platinum catalyst required several hours. The product from a large-scale hydrogenation was isolated in ether after dilution of the acetic acid solution with water. Evaporation of the ether left a solid residue, which was crystallised several times from ethanol at 0° as colourless plates, m. p. 65·2—66·8° (Found: C, 76·6; H, 12·8%; equiv., 298, 296. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·8%; equiv., 298·5). The m. p. was 63—66·5° after one recrystallisation.

Oxidation of Sterculic Acid with Potassium Permanganate.—Sterculic acid (5·0 g.) in pure dry boiling acetone (70 c.c.) was treated with finely powdered potassium permanganate (14 g.) in small quantities during 1·5 hours. The acetone was then distilled off on a water-bath. The distillate was clear when diluted with water and was discarded. The residue was diluted with

water, and sulphur dioxide was passed in to dissolve the manganese dioxide, after which the mixture was steam-distilled, 750 c.c. of distillate being collected. The distillate, neutralised with sodium carbonate, was extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract left an oil (0·3 g.), which gave no ketone reactions. The alkaline solution, remaining after the ether-extraction, was concentrated to about 100 c.c., acidified with sulphuric acid, and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract left an oil (0·94 g.), which was distilled to yield a colourless acid (0·56 g.) as the main fraction, b. p. 230—235°/655 mm. The remainder of the material, a high-boiling tar, decomposed on further heating. The *p*-bromophenacyl ester of the above acid crystallised in colourless plates (from ethanol), m. p. 62—63·3° alone or mixed with *p*-bromophenacyl pelargonate (Found: C, 57·4; H, 6·6. Calc. for $C_{17}H_{23}O_3Br$: C, 57·5; H, 6·5%).

The residue from the steam-distillation was extracted with ether and this solution in turn was extracted with sodium carbonate solution. Evaporation of the dried (Na_2SO_4) neutral ethereal extract left an oil (20 mg.) which was discarded. The sodium carbonate extract was acidified and the precipitate isolated in ether. Evaporation of the ether from the dried (Na_2SO_4) extract gave a semi-solid acid (2·83 g.). The methyl ester, made by treatment with diazomethane in ether, was distilled, yielding, as main fraction, a pale yellow oil (0·8 g.), b. p. 85—89°/0·1 mm. The remainder of the material distilled at 177—200°/0·1 mm., with much decomposition, giving a viscous red oil (1·2 g.). The first fraction was hydrolysed and the acid (0·62 g.) crystallised from water in large colourless leaflets, m. p. 106—108° alone or mixed with azelaic acid (Found: C, 57·5; H, 8·6%; equiv., 93·8, 94·4. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%; equiv., 94·1). Hydrolysis of the second fraction yielded a liquid acid which proved to be mainly polymerized sterculic acid.

In order to ensure that no other dibasic acid was present, all the aqueous solutions above were extracted continuously with ether for several hours. Traces of azelaic acid only were recovered.

Ozonolysis of Sterculic Acid.—(i) *In acetic acid.* Into a solution of sterculic acid (3·3 g.) in acetic acid (70 c.c.) was passed ozonised oxygen at 300 c.c./min. (*ca.* 0·0093 g. of ozone/min.) for 30 minutes. The solution was cooled in ice-water when the temperature tended to rise. At the end of the reaction, hydrogen peroxide (2 c.c.; 140-vol.) was added and the mixture heated on a water-bath. After 1 hour more hydrogen peroxide (4 c.c.) was added and again after 2 hours (2 c.c.). Heating was stopped after 4 hours and the solution left overnight; it was then refluxed for 1 hour and steam-distilled, 600 c.c. of distillate being collected.

The distillate, made alkaline with sodium hydroxide, was extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal solution yielded an oil (10 mg.) which was discarded. The aqueous layer was acidified and extracted with ether. Evaporation of the solvent afforded an oil which, on distillation, gave some acetic acid and pelargonic acid (0·5 g.), b. p. 238—140°/655 mm., only (Found: C, 68·1; H, 11·4%; equiv., 156. Calc. for $C_9H_{18}O_2$: C, 68·3; H, 11·5%; equiv., 158·2). The *p*-bromophenacyl ester crystallised in plates (from ethanol), m. p. 63—63·8° alone or mixed with *p*-bromophenacyl pelargonate (Found: C, 57·6; H, 6·6; Br, 22·0. Calc. for $C_{17}H_{23}O_3Br$: C, 57·5; H, 6·5; Br, 22·5%). The amide crystallised in leaflets (from aqueous methanol), m. p. 98·5—99·5° alone or mixed with pelargonamide.

The residue from the steam-distillation was extracted with ether and this solution in turn was extracted with sodium hydrogen carbonate solution. Evaporation of the dried (K_2CO_3) ethereal solution left an oil (0·15 g.) which gave no ketone reactions and was discarded. The sodium hydrogen carbonate solution was boiled until free from ether and acidified. The solid acid (1 g.) was filtered off, dried, and esterified with diazomethane in ether. Evaporation of the ether and distillation of the ester gave a colourless oil, b. p. 152—153°/20 mm., together with a small quantity of tar. The ester was hydrolysed and the acid crystallised from water in large colourless plates, m. p. 106—108° alone or mixed with azelaic acid. No other dibasic acid could be detected in any of the aqueous solutions.

(ii) *In ethyl acetate.* Ozonised oxygen was passed into sterculic acid (1·41 g.) in anhydrous ethyl acetate (35 c.c.) at −25° (rate as above) for 30 minutes, care being taken to avoid an excess of ozone by testing the effluent gas at regular intervals. At the end of the reaction 30% palladised charcoal was added to the solution which was cooled in ice-water and hydrogenated. Hydrogenation was complete in 5 hours, 89·5 c.c. of hydrogen (N.T.P.) (87% of theory) being absorbed. The catalyst was filtered off and the solvent distilled. The distillate was refluxed with 2 : 4-dinitrophenylhydrazone (0·5 g.) in ethanol (50 c.c.) and hydrochloric acid (0·5 c.c.) for 2·5 hours, and then evaporated to a small volume (5 c.c.). To this were added ethanol (50 c.c.) and hydrochloric acid (0·5 c.c.). After storage overnight in the ice-box, the

orange crystals (0·18 g.) were filtered off, dried, and then chromatographed in benzene on alumina. Concentration of the eluate gave flattened orange needles which, recrystallised from ethanol, had m. p. 164—167° alone or mixed with formaldehyde 2 : 4-dinitrophenylhydrazone (Found : C, 40·4; H, 3·0. Calc. for $C_7H_6O_4N_4$: C, 40·0; H, 2·9%). The solid residue remaining after removal of the ethyl acetate was dissolved in ether (150 c.c.) and extracted with sodium hydrogen carbonate solution. An insoluble sodium salt, which was precipitated, was filtered off. The neutral ethereal solution was evaporated, leaving an oil (0·22 g.), which had no ketonic reactivity and distilled with decomposition at 150—300°/650 mm. It was discarded. The sodium hydrogen carbonate extract and the insoluble sodium salt were combined and acidified, the liberated acid being isolated in ether. Evaporation of the ether left 9 : 11-*diketononadecanoic acid* as a solid (1·1 g.) which crystallised from 2-methylpentane in long colourless needles, m. p. 57·5—58·3° (Found : C, 69·8; H, 10·5. $C_{19}H_{34}O_4$ requires C, 69·9; H, 10·5%). This substance gave a deep red colour with ferric chloride in ethanol. It could not be titrated with sodium hydroxide to a definite end-point to phenolphthalein, and values varying from 250 and 285 were obtained for the equivalent weight. It did not form a semicarbazone.

Oxidation of 9 : 11-*Diketononadecanoic Acid* (II)—The substance was oxidised rapidly by potassium permanganate in acetone solution, but the product was an ether-insoluble polymer.

A mixture of 9 : 11-diketononadecanoic acid (0·5 g.), acetic acid (10 c.c.), and hydrogen peroxide (1 c.c.; 140-vol.) was heated on a water-bath for 1 hour. Hydrogen peroxide (1·5 c.c.) was then added and the solution refluxed for a further hour. Steam-distillation afforded a volatile acid and no volatile neutral material. Distillation of the acid gave an oil (0·2 g.), b. p. 240°/650 mm. The *p*-bromophenacyl ester had m. p. 61·5—62·5° alone or mixed with *p*-bromophenacyl pelargonate. The residue from the steam-distillation contained no neutral material; it was extracted with ether and this solution treated with an ethereal solution of diazomethane. The residue (0·37 g.) obtained after evaporation of the ether was distilled (b. p. 150—153°/20 mm.). Hydrolysis of the distillate and crystallisation of the acid from water gave azelaic acid, m. p. and mixed m. p. 105—108°.

Sterculyl Alcohol.—Sterculic acid (7·3 g.) was reduced with lithium aluminium hydride (2·7 g.) in ether (150 c.c.) in the usual manner. The *alcohol*, recrystallised from acetone at −35° and dried at room temperature in a high vacuum, had m. p. 10·6°, n_D^{30} 1·4617 [Found : C, 80·9; H, 12·9%; active H (by $LiAlH_4$ method, Hochstein, *loc. cit.*) 1·02 atoms. $C_{19}H_{36}O$ requires C, 81·3; H, 12·9%; active H, 1·0 atom]. With palladised calcium carbonate, the alcohol (30·66 mg.) absorbed 2·50 c.c. of hydrogen (N.T.P.) ($C_{19}H_{36}O$ requires 2·45 c.c.), and with Adams's platinum catalyst it (15·66 mg.) absorbed 2·77 c.c. (N.T.P.) ($C_{19}H_{36}O$ requires 2·50 c.c.). An attempt to distil the alcohol resulted in extensive decomposition with the formation of a viscous, liquid distillate, b. p. 143—155°/0·4 mm., which was not investigated.

The analyses were carried out in our Microchemical Department by Mr. F. W. G. Schöning and Mrs. V. Maritz. The author is grateful to Drs. D. A. Sutton and W. S. Rapson for many helpful discussions. This paper is published with the permission of the South African Council for Scientific and Industrial Research.

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Pretoria, South Africa.

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67. *Structure of Molecular Compounds. Part X.* Crystal Structure of the Compound of Benzene with an Ammonia–Nickel Cyanide Complex.*

By J. H. Rayner and H. M. Powell.

The compound $Ni(CN)_2,NH_3,C_6H_6$ has a tetragonal unit cell, $a = 7{\cdot}24$, $c = 8{\cdot}28$ Å, which contains atoms corresponding to twice this formula. Covalencies link nickel atoms through CN groups to form an extended flat network. Half the nickel atoms have four cyanide carbon atoms attached by square bonds. The metal-to-carbon distance indicates some double bonding between these atoms. The other nickel atoms are linked to four nitrogen atoms of CN groups in the form of a square, and to two ammonia groups which complete an approximately regular octahedron of nitrogen atoms. The distances nickel-to-nitrogen correspond to single bonds. Layers of this structure are arranged parallel to each other and between them are benzene molecules with their planes at right angles to that of the layers. Each benzene molecule is comparatively remote from nickel atoms. It is contained in a cavity where it makes contacts at van der Waals distances with other benzene molecules and with atoms of cyanide and ammonia groups. It is not linked by chemical bonds to the nickel complex. Some observations on related compounds are recorded.

When benzene is added to a solution of nickel cyanide in aqueous ammonia a precipitate of the composition $Ni(CN)_2,NH_3,C_6H_6$ is formed (Hofmann and Küspert, *Z. anorg. Chem.*, 1897, **15**, 204). Similar compounds are formed by such other aromatic substances as pyrrole, furan, thiophen, pyridine, phenol, and aniline. Hofmann and Arnoldi (*Ber.*, 1906, **39**, 339) pointed out the comparatively small molecular volumes of these aromatic substances and found that similar compounds are not formed by fluorobenzene or other aromatic compounds of molecular volumes above a certain value.

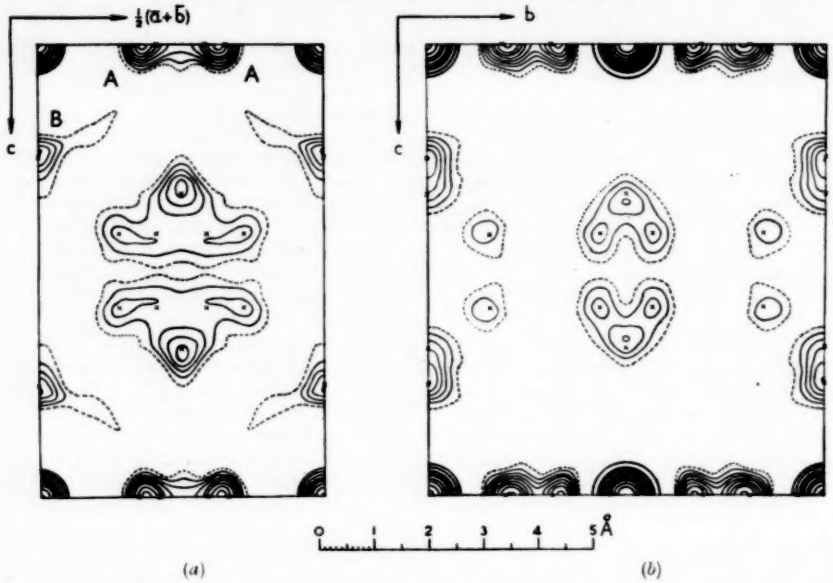
The benzene in the compound is very firmly retained, there being no detectable pressure at room temperature. Some of it may be removed by repeated washing with ether and it is evolved when the compound is heated to 120°.

Speculations such as those of Pfeiffer ("Organische Molekülverbindungen," 2nd edn., Stuttgart, 1927, p. 213) and of Feigl (*Anais Assoc. Quím. Brasil*, 1944, **3**, 72) in which benzene molecules are supposed to occupy positions in the co-ordination sphere of the nickel atom do not provide a satisfactory formulation for the compound. Reasons for supposing that it might be a molecular compound have already been given and a preliminary account of the structure has appeared (Powell and Rayner, *Nature*, 1949, **163**, 566).

A detailed *X*-ray structural investigation requires single crystals much larger than any present in the microcrystalline substance obtained by the method mentioned above or by the modified procedure due to Hofmann and Höchtlen (*Ber.*, 1903, **36**, 1149), in which acetic acid is added to the ammoniacal nickel cyanide solution. Ordinary methods of recrystallisation are inapplicable but the formation of larger crystals might be achieved by slowing down the precipitation process. Omission of acetic acid from a solution otherwise the same as that used by Hofmann and Höchtlen has the desired effect. Such a solution left in contact with a layer of benzene deposits in a few days crystals which are recognisable under the microscope as square plates with bevelled edges. The speed of formation of crystals may be further reduced by dilution of the ammoniacal nickel cyanide solution with its own volume of water and of the benzene with its own volume of xylene. Xylene can be used because it does not replace benzene in the compound. One such preparation extending over 75 days gave crystals in the form of square plates with sides of up to 0·5 mm. and of thickness up to 0·12 mm. Some of these were used for the *X*-ray examination.

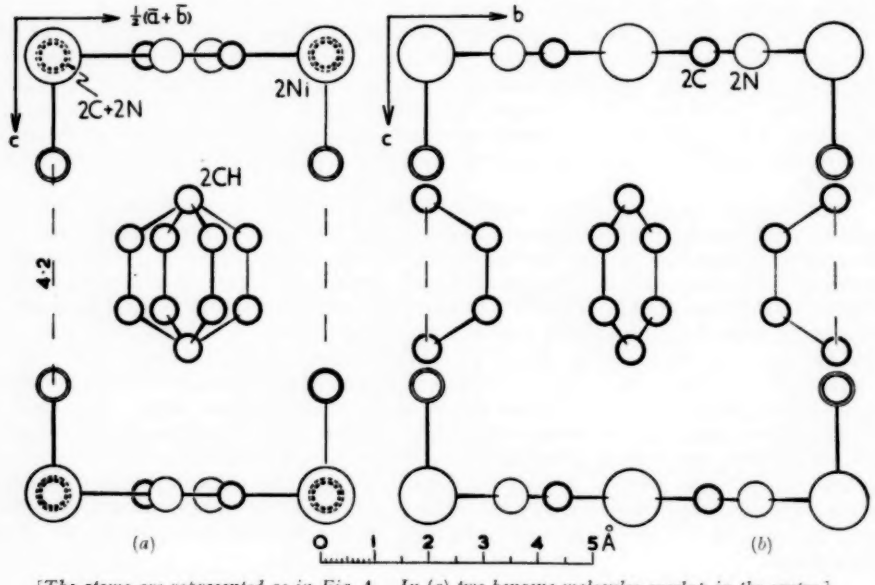
* Part IX, *J.*, 1950, 468.

FIG. 1. *Electron-density projections on* (*a*) (110) *and* (*b*) (100).



In (*a*) *the highest peaks, which represent* 2Ni + 2C + 2N, *have contours at* 20, 40, *etc., electrons*/Å^3. *In* (*b*) *the highest peaks, which represent nickel atoms, have contours at* 5, 10, *etc., electrons*/Å^2. *In other parts of both projections contours are drawn at intervals of* 2 *electrons*/Å^2. *The lowest shown is at* 4 *electrons*/Å^2. *Crosses indicate the positions of atoms determined after corrections for effects due to non-termination of Fourier series.*

FIG. 2. *Positions of atoms corresponding to Figs.* 1(*a*) *and* (*b*).



[*The atoms are represented as in Fig.* 4. *In* (*a*) *two benzene molecules overlap in the centre.*]

The crystals which appear mauve to the eye are tetragonal, tabular on (001) with cleavages parallel to (001) and (110). Other faces for which approximate interfacial angles are observable under the microscope are {110} and {111}. The crystals are optically uniaxial with negative birefringence. They are pleochroic: when the electric vector is parallel to *c* the light transmitted is green; when it is at right angles to *c* the light is purple. No pyroelectric effect was observed. The density by flotation is 1·58 g./c.c.

For *X*-ray examination the radiation from a copper target was filtered through nickel foil. Single-crystal oscillation photographs were obtained by both the stationary-film and the Weissenberg method. In the Weissenberg procedure zero layers were photographed for oscillation about the [110] and [100] axes. Exposure times were varied and in each exposure three films were loaded together in the camera so that an intensity range of 1—2000 could be covered.

The intensities of the reflections were measured by visual comparison with a scale of spots of known exposure. Because the crystal was a flat plate the reflected spots varied in size and shape on different parts of the film, and in the case of the *hhl* reflections a correction for this was made in the way used by Broomhead (*Acta Cryst.*, 1948, **1**, 324) for a crystal of similar shape.

The film is divided into strips in which the spots are all of about equal size. Spots which by tetragonal symmetry must have equal intensity (*i.e.*, $I_{hkl} = I_{\bar{k}hl}$) are found in different strips, so that all the strips can be compared. The factors relating intensities in one strip to those in another had values between 1 and 1·8.

These *X*-ray measurements confirm that the crystals belong to the tetragonal system. The cell dimensions are $a = 7{\cdot}242 \pm 0{\cdot}007$, $c = 8{\cdot}277 \pm 0{\cdot}008$ Å, and the calculated mass of the unit cell corresponds to 1·98 times the formula $Ni(CN)_2,NH_3,C_6H_6$. Since no class of reflections is found to be systematically absent the space group must be $P\bar{4}$, $P4$, $P4/m$, $P\bar{4}2m$, $P4mm$, $P42$, or $P4/mmm$. The last four are excluded by intensity relations among the observed reflections, which show that there are no vertical planes of symmetry or horizontal two-fold axes. Thus for a few pairs of reflections, the intensities of *hkl* and $\bar{h}kl$ are clearly unequal. This may be seen most readily by a comparison of spots related symmetrically to each other above and below the zero layer line on oscillation photographs taken with [100] as oscillation axis. Although the structure as a whole lacks this symmetry many of the atoms must lie in special positions which conform to it, because for many such pairs of reflections no difference is observable. If the crystals are centrosymmetric, as is suggested by the pyroelectric test, the space groups must be $P4/m$. The structure was developed in the first place on this assumption, but, if any other of the seven space groups enumerated above is taken as a basis, either the atomic positions deduced are the same as those in $P4/m$, or a too high symmetry such as that of $P4/mmm$ restricts the position of the benzene and makes it impossible to obtain agreement between observed and calculated intensities of reflection.

The two nickel atoms in each unit cell must occupy special positions on four-fold or two-fold axes of symmetry. Odd-layer lines of oscillation photographs about [110] are weaker than even-layer lines. This suggests that the nickel atoms, which represent about a quarter of the scattering power of the cell contents, are disposed so that, as far as they are concerned, the (001) face is centred. For any such arrangement the nickel atoms must be in symmetry centres. It is therefore possible to select a unit-cell origin at the centre of a nickel atom and to evaluate Fourier series for electron density. This was done for the *hhl* structure factors and a projection on (110) was thus obtained. All the structure factors were given positive signs as though they were due to the nickel contributions alone.

In the projection [Fig. 1(*a*)] two peaks *A* are found between each pair of nickel atoms. They are in positions consistent with a structure made up of a square network parallel to (001), having nickel atoms at the corners and CN groups along the sides. In the view provided by this projection each of these peaks represents the overlap of a carbon and a nitrogen atom. The side of the square network is 5·1 Å, a distance appropriate to a linear Ni–CN–Ni arrangement. The carbon and the nitrogen atoms occupy special four-fold positions $xy0$, and for the arrangement described x and y are equal.

Peaks *B*, lying along the *c* direction about 2 Å above and below the nickel peaks, suggest that ammonia groups are attached to the nickel atoms in some way. Since there are only two of these groups per unit cell, they can only occupy the positions 00z, 00z or $\frac{1}{2}\frac{1}{2}z$, $\frac{1}{2}\frac{1}{2}\bar{z}$, and the line parallel to *c* on which they lie must be a four-fold axis. It follows that the unit-cell origin (selected at a nickel atom) must also lie on a four-fold axis. The nickel atoms therefore occupy two non-equivalent special positions 000 and $\frac{1}{2}\frac{1}{2}0$ and one of these must have two attached ammonia groups. Equivalent structures result from either choice and the nickel atom at 000 has been selected as the one having attached ammonia groups.

The two benzene groups must lie in special positions and of these only $0\frac{1}{2}0$, $\frac{1}{2}00$ and $0\frac{1}{2}\frac{1}{2}$, $\frac{1}{2}0\frac{1}{2}$ are possible on symmetry grounds. The remaining well-defined areas of electron density in the projection can only be explained if the benzene molecules have their centres at $0\frac{1}{2}\frac{1}{2}$ and $\frac{1}{2}0\frac{1}{2}$. Benzene molecules are thus shown to be in these positions, with a two-fold symmetry axis parallel to [001], and a plane of symmetry perpendicular to this axis. Of the three ways in which this could be achieved by a regular hexagon, that with two carbon atoms on the two-fold axis is seen directly from the projection to be correct. Two carbon atoms of each benzene ring are on the two-fold axes at $0\frac{1}{2}z$ and its equivalents, and the remaining carbon atoms in general positions *xyz*. The values of x and y cannot be determined from the (110) projection since the tetragonal symmetry brings about an overlap of two benzene molecules in different orientations and with centres at $0\frac{1}{2}\frac{1}{2}$ and $\frac{1}{2}0\frac{1}{2}$. This overlap is avoided in the projection on (100).

The 0*kl* structure factors were obtained from approximate co-ordinates that could now be deduced, the chief uncertainty being in the *xy* co-ordinates of the carbon atoms in general positions. In this and later structure factor calculations the atomic scattering curve used for nickel was that given by Robertson for nickel phthalocyanine (*J.*, 1936, 1195) which was investigated with Cu-K_α radiation. For the benzene carbon atoms scattering factors were taken from Robertson's values for hydrocarbons (*Proc. Roy. Soc.*, 1935, *A*, **150**, 106), but for the carbon and nitrogen atoms which are very tightly bound in the cyanide complex James and Brindley's curves (*Phil. Mag.*, 1931, **12**, 81) were employed. This choice resulted from trials with the 00*l* series of reflections.

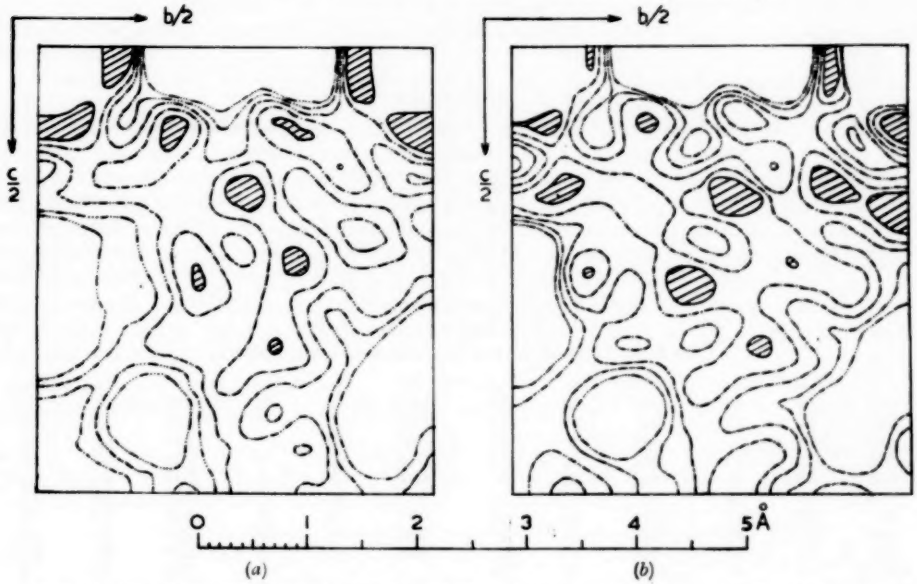
The signs thus obtained were used in the F0*kl* electron-density synthesis. The resulting projection [Fig. 1(*b*)] confirmed the general structure proposed, showed separately the nitrogen and carbon atoms which overlapped in the (110) projection, and gave the y co-ordinates of the eight carbon atoms in the general positions It failed through imperfect resolution to give their x values and, owing to overlap with NH_3 groups, did not resolve the benzene carbon atoms on the two-fold symmetry axes. Since some changes of parameters are suggested by the projection, signs were recalculated to allow for this, and the synthesis was repeated with the inclusion of ten small terms which had previously been omitted owing to uncertainty in their signs. The general appearance of the projection was not changed but improved values of some of the parameters could be obtained. The atomic positions corresponding to the projections 1(*a*) and (*b*) are shown in Figs. 2(*a*) and 2(*b*) which are based on the final corrected parameters given below.

Since reflections at high angles are very strong it seemed probable that the calculated electron-density maps would show errors due to non-convergence of the Fourier series, and this was confirmed by a Fourier synthesis carried out with the calculated structure factors as coefficients. The results of the summations with observed and with calculated coefficients are shown in Figs. 3(*a*) and 3(*b*). In these, contours are given only for the areas of low electron density which do not correspond to atoms. They have the same general form in both and may therefore be ignored in the projection derived from the observed structure factors. The positions of the atomic peaks are however affected by these diffraction effects and a comparison of the peak positions in the two permits correction in the manner suggested by Booth (*Proc. Roy. Soc.*, 1946, *A*, **188**, 77).

With the best parameters now available the structure factors were recalculated. Improvements in the agreement between the observed and calculated structure factors were found. The sign of the calculated F_{081} had changed and this was allowed for, but all F_{hkl} remained positive as they had been taken in the first projection. The newly

calculated structure factors were used for further Fourier synthesis of F_{hkl} and F_{0kl}. The F_{hkl} synthesis was compared with that calculated from the observed values, and corrections were made to the atomic co-ordinates. The F_{0kl} synthesis was similarly used to make a more accurate correction than that based on the synthesis with the former set of calculated

FIG. 3. *The lower contours in the electron-density projection on* (100).



Part (*a*) *shows the contours derived from observed* F's *and corresponds to Fig.* 1(*b*). *The higher contours are omitted, the highest shown being identical with the lowest of Fig.* 1(*b*). *Contours are at intervals of* 1 *electron*/Å^2 *and the shaded areas show negative regions.*

Part (*b*) *is the similar projection derived from the calculated* F *values. Negative regions and areas of appreciable electron density not attributable to atoms occur in approximately the same positions in* (*a*) *and* (*b*).

F_{0kl}. The small changes in co-ordinates resulted in a change of sign in the small term F_{030} and so the process of correction was repeated for this projection. The parameters derived by consideration of both projections are listed in Table 1. These lead to the interatomic distances of Table 2. These are not all of the same probable accuracy.

TABLE 1. *Atomic co-ordinates.*

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Ni(1)	0	0	0	C(1)	0·328(5)	0·328(5)	0
Ni(2)	½	½	0	C(2)	0	½	0·330
N(1)	0·209(6)	0·209(6)	0	C(3)	0·153	0·435	0·417
N(2)	0	0	0·249				

In Figs. 1(*a*) and 2(*a*) the peak at the origin represents 2Ni + 2C + 2N. The Ni–N (of NH_3) bond length is given by the distance from the origin to a small peak representing a single NH_3 group. The position of the small peak is subject to a large diffraction correction (0·07 Å) compared with those in the (100) projection. In this projection [Figs. 1(*b*) and 2(*b*)] the larger peaks represent single nickel atoms and carbon atoms of CN appear as peaks due to the overlap of two C atoms with the same projected co-ordinates. The nitrogen atoms of CN similarly overlap. For Ni–N (of CN) and Ni–C the probable error is ±0·03 Å while for N–C it is ±0·04 Å. The benzene C–C distances are less accurate since separate determinations of all the co-ordinates are impossible owing to over-lapping.

The most reliable of these distances is 1·38 Å for C(3)–C(3) which can be measured directly in the (100) projection. The Ni–NH_3 distance is considered the least reliable since the differences in shape and position of the NH_3 peak in the " observed " and " calculated " syntheses are greater than for any other peak.

Calculated structure factors and the observed values adjusted to the same scale are given in Table 3.

The value of

$$R = \frac{\Sigma||F_{obs.}| - |F_{calc.}||}{\Sigma|F_{obs.}|}$$

TABLE 2. *Interatomic distances.*

Bond lengths

Atoms	Å
Ni(1)–N(1) of CN	2·15
Ni(1)–N(2) of NH_3	2·06
Ni(2)–C(1) of CN	1·76
C(1)–N(1)	1·22
C(2)–C(3)	1·41
C(3)–C(3)	1·38

Non-bonded distances

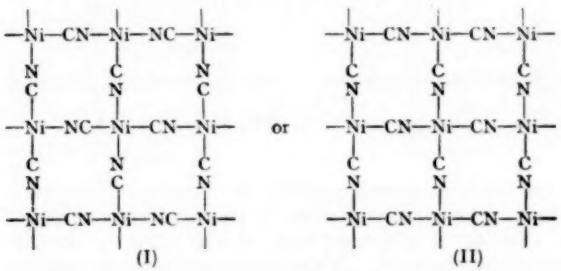
Atoms	Å
C(2)–N(2)	3·7
C(2)–N(1)	3·8
C(2)–C(1)	3·8
C(3)–N(2)	3·6
C(3)–C(3)	3·6
C(3)–C(1)	3·75
C(3)–N(1)	3·8
N(2)–N(2)	4·2

TABLE 3. *Observed and calculated structure factors.*

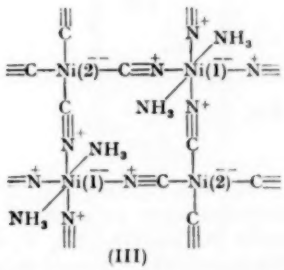
hkl	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$	*hkl*	$F_{obs.}$	$F_{calc.}$
001	34	45	040	35	37	080	12	10	330	51	43
002	54	73	041	35	36	081	8	4	331	49	48
003	71	81	042	21	16	082	<2	−1	332	48	36
004	55	53	043	36	34	083	10	6	333	35	32
005	60	57	044	30	31	084	8	5	334	38	46
006	36	29	045	17	15				335	33	34
007	39	41	046	24	24	090	8	13	336	20	21
008	28	32	047	14	12	091	6	10	337	29	26
009	29	30	048	17	18	092	4	6	338	29	30
0.0.10	17	21	049	12	14				339	15	17
						110	28	27			
010	7	4	050	13	14	111	62	72	440	41	41
011	6	2	051	<2	1	112	31	29	441	29	16
012	18	−14	052	<2	1	113	30	27	442	24	17
013	<2	1	053	<3	4	114	41	55	443	27	25
014	12	8	054	6	7	115	27	26	444	23	22
015	8	−2	055	<3	5	116	24	19	445	18	20
016	7	−4	056	<3	2	117	24	20	446	19	10
017	<3	−2	057	<3	4	118	25	27	447	17	15
018	<3	3	058	<2	5	119	12	13	448	12	14
019	<3	−2	059	2	2	1.1.10	11	10			
0.1.10	<2	2							550	29	28
			060	32	36	220	70	74	551	31	30
020	48	45	061	26	26	221	56	47	552	26	22
021	<1	3	062	23	20	222	37	31	553	22	23
022	6	1	063	29	29	223	46	51	554	26	31
023	25	25	064	24	27	224	37	44	555	23	23
024	14	14	065	20	20	225	26	30	556	17	15
025	12	10	066	22	20	226	30	29			
026	13	9	067	16	17	227	23	24	660	18	22
027	9	6	068	12	18	228	25	26	661	18	18
028	7	7				229	22	22	662	12	10
029	8	6	070	4	4	2.2.10	9	11	663	19	18
0.2.10	3	−2	071	12	−11				664	15	20
			072	6	−7						
030	6	−4	073	6	−5						
031	12	10	074	4	−4						
032	15	−13	075	<2	−1						
033	<2	0	076	11	−12						
034	10	10									
035	7	−4									
036	<3	2									
037	<3	−3									
038	<3	7									
039	<2	2									

is 0·20 for 0*kl* and 0·13 for *hhl* reflections. In addition to the agreement between calculated values of the structure factors used in Fourier syntheses, confirmation of the structure as a whole was obtained by the calculation of a number of *hkl* structure factors. For all the following pairs of reflections, observed on one oscillation photograph, the calculated intensity of the first was greater than that of the second, and in every case this was also true of the observed intensities: 131, $\bar{1}31$; $\bar{2}44$, 244; $\bar{1}55$, 155; $\bar{2}46$, 246; 245, $\bar{2}45$; $\bar{3}22$, 322; 232, $\bar{2}32$; $\bar{1}44$, 144; $\bar{1}42$, 142. The reflections from the planes 243 and $\bar{2}43$ were calculated to be very nearly equal and no difference could be detected in their photographed intensities.

Nickel atoms are linked by cyanide groups in an extended two-dimensional array to form a flat network. There is no great difference in peak heights for the carbon and the nitrogen atoms of the cyanide group. There is a similar lack of any striking distinction between these atoms in the electron-density map obtained from the calculated structure factors, but in both cases the peaks near to Ni(2) are lower than those near to Ni(1). Thus the observed structure factors agree with the supposition that four cyanide carbon atoms are attached to Ni(2). The distinction between these atoms and the four cyanide nitrogen atoms attached to Ni(1) is shown more clearly by the interatomic distances. The observed distances Ni–N = 2·15 and Ni–C = 1·76 Å are explained only if the links are between the atoms named. A difference in length would not appear if the symmetry resulted from some other ordered or disordered arrangement of layers such as (I) or (II) in which the corresponding peaks would be equal.



(I) (II)



(III)

In the structure deduced the nickel atoms are of two kinds: half are bonded to four cyanide carbon atoms in the plane of the network, the others form six octahedral bonds, four to cyanide nitrogen atoms and two, projecting above and below the network, to ammonia groups. A simple formulation of this complex is (III).

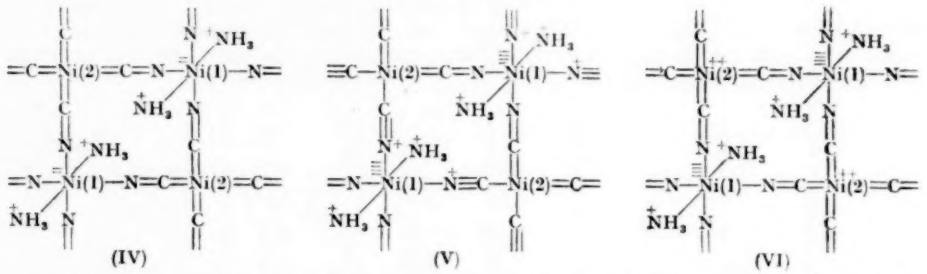
In various analogous complexes, such as nickel carbonyl (Brockway and Cross, *J. Chem. Physics*, 1935, **3**, 828), the hexamethyl*iso*cyanidoferrous ion (Powell and Bartindale, *J.*, 1945, 799), and the tetracyanonickelate ion (Brasseur and Rassenfosse, *Mem. Soc. Roy. Sci. Liège*, 1941, [2], **4**, 397; Lambot, *Bull. Soc. Roy Sci. Liège*, 1943, **12**, 522), there is evidence that the metal-to-carbon distances are shorter than might be expected for single bonds. There is no record of the nickel-to-carbon distance in any compound of planar four-covalent nickel in which there is no doubt of the single-bond character of the Ni–C link, but possible values may be estimated from bond lengths in other nickel compounds. Subtraction of the sulphur radius 1·04 from the nickel-to-sulphur distance 2·30 Å in potassium nickelodithio-oxalate (Cox, Wardlaw, and Webster, *J.*, 1935, 1475) gives a radius for nickel of 1·26 Å. Pauling obtained a similar value (1·22 Å) for the nickel radius ("Nature of the Chemical Bond," 2nd edn., Ithaca, New York, 1945, p. 251) by a more complex route, and though the derivation has been criticised (Wells, *J.*, 1949, 66) the radius obtained is not likely to be as much as 0·1 Å in error. These nickel radii require nickel-to-carbon distances of 1·99 or 2·03 Å. The observed value, 1·76, is less by 0·23, an amount so large compared with the possible errors that some multiple-bond character must be assumed.

The distance may be further considered in relation to the nickel-to-carbon distance in compounds where, although the bond multiplicity may not be known, there is no doubt

that at least a single bond is present. The work of Brasseur and others on the salts of the tetracyanonickelate ion indicates nickel-to-carbon distances of 1·85—1·9 Å. This length which must be less than, or equal to, the single-bond distance provides a check that the observed distance 1·76 Å is shorter than a single bond.

No similar shortening is found in the nickel-to-nitrogen distances which have been observed for octahedral nickel in $K_2Ca[Ni(NO_2)_6]$ (Driel and Verweel, *Z. Kryst.*, **1936**, **95**, 308) as 2·15 ± 0·03 Å. Alternatively Pauling's single-bond radii (*op. cit.*, pp. 182, 164) lead to 2·09 Å. The distances Ni–N 2·15 and Ni–NH_3 2·06 observed are both close to these values, and their difference from each other is not regarded as significant in view of larger probable error in the Ni–NH_3 distance.

The complex may be formulated in a number of ways consistent with these conclusions on bond multiplicity, for example, (IV), (V), and (VI). In (IV), every nickel atom has the effective atomic number of krypton; Ni(2) is isoelectronic with the nickel atom in $Ni(CO)_4$ and has zero valency, and Ni(1) has a valency of four. However this arrangement of bonds cannot be the principal one in this compound which is paramagnetic. It has a moment of 2·32 Bohr magnetons per nickel atom (Craig, Thesis, Univ. Sydney, 1942), which requires some nickel electrons with unpaired spins.



(IV) (V) (VI)

In both (V) and (VI), Ni(1) has the effective atomic number 38. Its two "surplus" electrons must be in 5*s* or 4*d* orbitals. The paramagnetism of the isoelectronic nickel atom in $[Ni(NH_3)_6]Cl_2$ is evidence that 4*d* is preferred and, if the same is true in this compound, it should be paramagnetic, as observed. If the only restrictions on possible bond orbitals are those summarised by Kimball (*J. Chem. Physics*, 1940, **8**, 188) then in (VI) and in some other arrangements, but not in (V), Ni(2) might also contribute to the paramagnetism.

Layers of the form described are arranged parallel to each other. As shown in Fig. 4, the ammonia groups projecting from one layer, imagined as horizontal, are vertically above and below those from the adjacent layers. This packing of the layers leaves a series of cavities each containing a benzene molecule.

The benzene carbon atom C(2) which lies on the two-fold symmetry axis is surrounded by two ammonia nitrogen atoms at 3·7 and by four cyanide carbon atoms C(1) at 3·8 and four cyanide nitrogen atoms also at 3·8 Å. Of these ten contacts those to one side of the atom are shown in Fig. 5. The symmetry permits any orientation of the molecule consistent with the two-fold axis, and that adopted gives the largest possible distances between the carbon atoms of the benzene and their surroundings. The benzene carbon atom C(3) in the general position has for neighbours two C(3) atoms of other molecules at 3·6, an ammonia nitrogen atom at 3·6, a cyanide carbon atom at 3·75, and a cyanide nitrogen atom at 3·8 Å. These large distances show that there is no chemical bond between the benzene molecules and the nickel complex. The substance must be described as a crystalline molecular compound.

In this it differs from the complex of benzene with silver perchlorate described by Rundle and Goring (*J. Amer. Chem. Soc.*, 1950, **72**, 5337). Short distances 2·6 Å from silver ions to carbon atoms are interpreted in terms of bonds of very low order.

Each layer of the structure has ammonia groups projecting above and below. To form a crystal these layers can only be packed parallel to each other, but the projecting

ammonia groups restrict their approach. If the projecting groups were staggered so that, as far as possible, they fitted between each other and not end to end, the layers could pack closer to each other, but the packing would still be poor. In the compound as formed with more widely separated layers, and benzene molecules occupying the cavities, there is very efficient space filling.

FIG. 4. *Part of structure to show surroundings of one benzene molecule.*

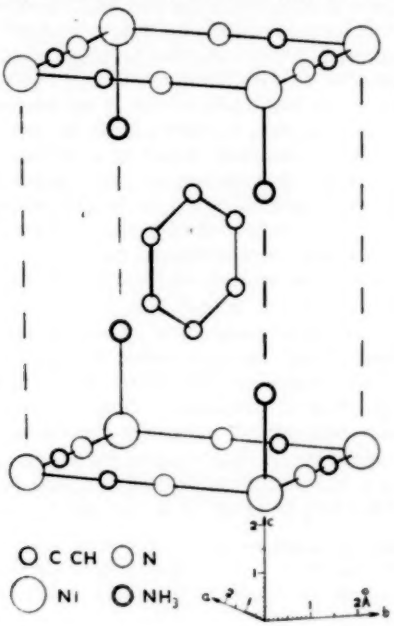
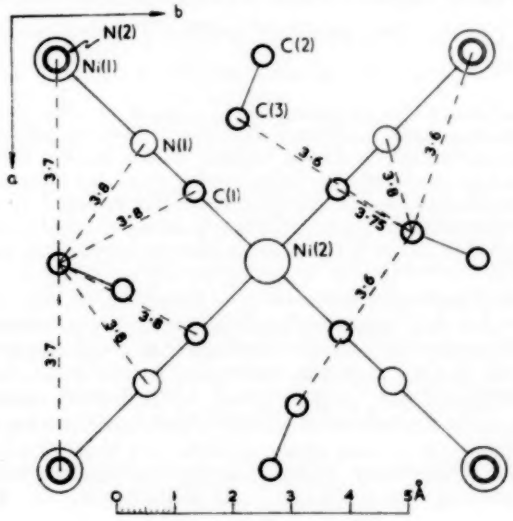


FIG. 5. *Structure projected on* (001) *to show non-bonded interatomic distances.*



Thiophen, pyrrole, furan, and pyridine, which form similar compounds, have molecules which are all somewhat similar in shape to that of benzene, but of slightly smaller volume. These substances, therefore, should replace benzene without enlargement of the layer spacing. Crystals of the thiophen compound decompose fairly readily but have been examined, and within 1% have the same c spacing as the benzene compound. With the observed arrangement of layers, little contraction of c is possible since the ammonia groups of adjacent layers are nearly in contact.

The action of the complex structure in accepting for enclosure in its cavities only those molecules of suitable size and shape explains why xylene does not form a similar compound. It has been applied to prepare quantities of benzene of exceptionally high purity (Evans, Ormrod, Goalby, and Staveley, *J.*, 1950, 3346). This selectivity resembles that in the clathrate compounds of quinol, where small atoms or molecules are completely encaged; but since the nickel cyanide complex is linked only in two dimensions, there is the possibility of enlargement of the cavities by wider separation of the layers. If molecules of substituted benzene derivatives were contained in such cavities, the substituents would have to be linked to benzene C(2) atoms by bonds parallel to the c axis. Since the other benzene CH groups are already in contact with others of their own kind in neighbouring molecules, there is clearly no space for substituents on them.

In the case of the aniline compound such an enlargement of the interlayer spacing has been found. For this compound $c = 9{\cdot}29 \pm 0{\cdot}05$ Å, greater by about 1 Å than the corresponding distance in the benzene compound. There will be a limit to this expansion process since it creates fresh empty spaces between the ammonia groups which are no longer nearly in contact. In conditions comparable with those used for benzene it is found that toluene does not form a compound. It is possible that the amino-group of aniline, which might interact with nickel, influences the formation of its compound, but in any case the toluene molecule would require more space since the C–C is slightly longer than C–N link and there are the additional hydrogen atoms of the methyl group. The limit of extensibility may therefore lie below that required to accommodate this molecule.

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68. *New Cytotoxic Agents with Tumour-inhibitory Activity. Part I. Some Aziridinopyrimidine Derivatives.*

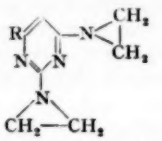
By J. A. HENDRY and R. F. HOMER.

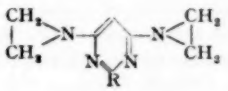
The reaction of ethyleneimine with a number of chloropyrimidines has given the corresponding aziridinopyrimidines. Those products which have in the molecule two ethyleneimine residues show a marked inhibiting effect on the growth of the Walker carcinoma 256 in rats, and cause abnormalities of the radiomimetic type in dividing cells. The nitration of a number of 2-aryl-4 : 6-dihydroxypyrimidines has been investigated, and some new 2-aryl-4 : 6-dichloro- and 2-aryl-4 : 6-dichloro-5-nitropyrimidines are described.

THE discovery in these and other laboratories of tumour-inhibitory and cytotoxic activity of the radiomimetic type in a number of cross-linking agents which also have the capacity to polymerise, for example, poly(hydroxymethylamides) and bis(ethylene oxides) (Rose, Hendry, and Walpole, *Nature*, 1950, **165**, 993; *Brit. J. Pharmacol.*, 1951, **6**, 201; Hendry, Homer, Rose, and Walpole, *ibid.*, p. 235; Ross, *J.*, 1950, 2257), has led us to examine a number of ethyleneimine derivatives as further examples of this type of compound. As various aziridinotriazines have been shown to have this type of activity (Rose, Hendry, and Walpole, *loc. cit.*; Burchenal, Stock, Crossley, and Rhoads, *Cancer Res.*, 1950, **10**, 207; Burchenal, Johnston, Stock, Crossley, and Rhoads, *ibid.*, p. 208), work on similar

derivatives of the biologically important pyrimidine nucleus followed, and this paper describes their preparation.*

The reaction between ethyleneimine and chloropyrimidines has been found to proceed readily in the presence of alkali, according to the method worked out by Bestian (*Annalen*, 1950, **566**, 210) for other compounds containing active chlorine atoms, provided that the halogen is sufficiently activated by the remainder of the molecule for reaction to occur under conditions which do not lead to polymerisation of the ethyleneimine or of the product. Thus, for example, 4 : 6-dichloro-5-nitropyrimidines react vigorously with ethyleneimine in the cold, both chlorine atoms being replaced; however, with un-nitrated 4 : 6-dichloropyrimidines only one chlorine atom reacts. Of the three chlorine atoms of 2 : 4 : 6-trichloropyrimidine only two can be replaced by ethyleneimine residues, giving 2 : 6-diaziridino-4-chloropyrimidine (I; R = Cl) and all attempts to replace the third chlorine atom by more drastic treatment have led to polymer formation. However, 2 : 6-diaziridino-4-chloropyrimidine reacts readily with sodium alkoxide, yielding (I; R = OAlk). The use of *N*-lithioethyleneimine as a reagent for relatively unreactive chlorine atoms, in accordance with the method of Gilman, Crounse, Massie, Benkeser, and Spatz (*J. Amer. Chem. Soc.*, 1945, **67**, 2106) has succeeded in a few cases, leading to (II; R = Ph and β-$C_{10}H_7$). It has not been possible to replace the third chlorine atom of trichloropyrimidine by this procedure.

(I) 

 (II)

The reaction of a chloropyrimidine with ethyleneimine is best carried out in aqueous alkali, or in benzene in the presence of triethylamine. The optimum reaction temperature appears to be between 30° and 45°, higher temperatures leading to polymerisation either of the ethyleneimine or of the product. It is essential that the reaction mixture at no time becomes acid as this leads to polymerisation or opening of the aziridine ring according to the conditions; the products are, however, stable to alkali, and in most cases can be recrystallised from moderately low-boiling solvents. The pure crystalline products are stable at room temperature for many months.

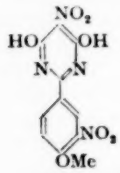
Starting materials were prepared by established general methods. Nitration of the hydroxypyrimidine was rapidly effected with fuming nitric acid in the cold, except in the case of 4 : 6-dihydroxy-2-β-naphthylpyrimidine where fuming acid caused decomposition and nitration was effected with a large excess of ordinary concentrated acid. In the case of 4 : 6-dihydroxy-2-*p*-methoxyphenyl-, 2-*p*-ethoxyphenyl-4 : 6-dihydroxy-, and 4 : 6-dihydroxy-2-*p*-tolyl-pyrimidine two nitro-groups were introduced by this treatment, one at position 5 of the pyrimidine ring and one in the aryl moiety. 4 : 6-Dihydroxy-2-phenyl- and -2-β-naphthyl- and 2-*p*-chlorophenyl-4 : 6-dihydroxy-pyrimidine yielded the 5-mononitro-compounds.

The nitro-group of the mononitro-compounds, and one of the nitro-groups of the dinitro-compounds, is at position 5 of the pyrimidine ring since, whereas the un-nitrated 2-aryl-4 : 6-dihydroxypyrimidines couple in alkaline solution with diazotised *p*-chloroaniline, and also give a yellow colour on treatment with nitrous acid (indicative of a free 5 position, Lythgoe, Todd, and Topham, *J.*, 1944, 315), the nitrated compounds undergo neither of these reactions. Direct proof of the structure of 4 : 6-dihydroxy-2-(4-methoxy-3-nitrophenyl)-5-nitropyrimidine (III) is afforded by oxidation with alkaline permanganate to 4-methoxy-3-nitrobenzoic acid. Similar oxidation of 4 : 6-dihydroxy-5-nitro-2-phenylpyrimidine yielded benzoic acid. The position of the nitro-group in the aryl moiety of 4 : 6-dihydroxy-2-(nitro-*p*-tolyl)-5-nitropyrimidine cannot be found by this method and has not been determined.

The crude hydroxynitropyrimidines which were too insoluble to crystallise in bulk,

* Patents pending.

though analytical samples were recrystallised satisfactorily from aqueous dimethylformamide, were converted smoothly into the corresponding, readily purified 2-aryl-4 : 6-dichloro-5-nitropyrimidines on treatment under reflux with phosphoryl chloride in the presence of dimethylaniline. Direct nitration of 4 : 6-dichloro-2-*p*-ethoxyphenylpyrimidine was effected in low yield by treatment with fuming nitric acid, one nitro-group only being introduced, presumably in the ethoxyphenyl residue, to give 4 : 6-dichloro-2-(4-ethoxy-3-nitrophenyl)pyrimidine (IV).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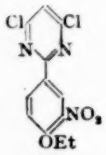
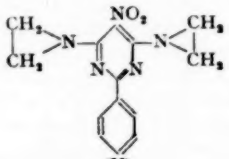

(IV)


(V)

4 : 6-Diaziridino-5-nitro-2-phenylpyrimidine (V) was reduced catalytically over Raney nickel at atmospheric temperature and pressure, without scission of the imine ring, to 5-amino-4 : 6-diaziridino-2-phenylpyrimidine. A similar reduction attempted with 2 : 4-diaziridino-5-nitropyrimidine gave only intractable or polymeric material.

Of the compounds obtained many of those carrying two ethyleneimine residues have been found to inhibit the growth of the Walker carcinoma 256 to a marked extent, and to show cytotoxic properties of the radiomimetic type (cf. Hendry, Homer, Rose, and Walpole, *Brit. J. Pharmacol.*, 1951, **6**, 357).

Experimental

Reaction of 2 : 4 : 6-*Trichloropyrimidine with Ethyleneimine.*—(a) *With* 1 *molecular proportion of ethyleneimine.* A solution of ethyleneimine (4·70 g.) in water (50 c.c.) was added to a suspension of 2 : 4 : 6-trichloropyrimidine (20 g.) in water (125 c.c.) containing sodium carbonate (6·3 g., anhyd.), with stirring at 30—35°. The oily mass which separated solidified after about 20 minutes. The reaction mixture was stirred for a further 0·5 hour, and then filtered, and the solid well washed with water and with a small quantity of ice-cold methanol. Fractional crystallisation from light petroleum (b. p. 60—80°) gave as the least soluble fraction 2-*aziridino*-4 : 6-*dichloropyrimidine* (5·8 g.), m. p. 105° (Found : C, 37·8; H, 2·6; N, 22·3. $C_6H_5N_3Cl_2$ requires C, 37·9; H, 2·6; N, 22·1%), and from the mother-liquors long needles of the isomeric 6-*aziridino*-2 : 4-*dichloropyrimidine* (1·25 g.), m. p. 111° (Found : C, 37·4; H, 2·6; N, 22·0%). The isomers are tentatively assigned these structures by analogy of the m. p. with those of the isomeric aminodichloropyrimidines and dichloromethylaminopyrimidines investigated respectively by Büttner (*Ber.*, 1903, **36**, 2228) and Winkelman (*J. pr. Chem.*, 1927, **115**, 292).

(b) *With* 2 *or more molecular proportions of ethyleneimine.* 2 : 4 : 6-Trichloropyrimidine (20 g.) was added slowly to a solution of ethyleneimine (12·4 g., 2·5 mols.) and triethylamine (29 g., 2·5 mols.) in benzene (100 c.c.) with stirring and cooling to keep the temperature at 25—30°. The reaction mixture was stirred for a further 1·5 hours at 25—30° and then filtered from triethylamine hydrochloride. The filtrate on evaporation under reduced pressure below 35° gave a semi-solid residue of crude product which was repeatedly extracted with boiling light petroleum (b. p. 60—80°). The cooled extracts deposited 2 : 6-*diaziridino*-4-*chloropyrimidine* as colourless plates, m. p. 94—95° (9·5 g., 44%) (Found : C, 49·05; H, 4·75; N, 28·6; Cl, 17·85. $C_8H_9N_4Cl$ requires C, 48·8; H, 4·6; N, 28·5; Cl, 18·1%). Occasionally the syrupy residue from the light petroleum extract polymerised violently after decantation of the solvent, possibly owing to local overheating during the extraction.

Treatment of 2 : 6-*Diaziridino*-4-*chloropyrimidine with Ethyleneimine.*—The pyrimidine (1·96 g.) was heated in benzene (25 c.c.), triethylamine (2·0 g.), and ethyleneimine (0·86 g.) under reflux for 3 hours. The resulting solution was decanted from glassy polymer (1·1 g.) and was evaporated to dryness under reduced pressure. Recrystallisation of the residue gave unchanged material (0·93 g., 47·5%).

2 : 6-*Diaziridino*-4-*methoxypyrimidine.*—2 : 6-Diaziridino-4-chloropyrimidine (8·8 g.) was added to a solution of sodium (1·2 g., 1·1 atoms) in AnalaR methanol (80 c.c.). An immediate cloudiness developed and after 1 hour at 50° the reaction was complete. The reaction mixture

was filtered from sodium chloride and the filtrate evaporated below 40° to a solid residue which on crystallisation from light petroleum (b. p. 60—80°) gave 2 : 6-*diaziridino*-4-*methoxypyrimidine* (3·3 g.) as colourless prisms, m. p. 86°, b. p. 110—120°/0·2 mm. (Found : C, 56·5; H, 6·5; N, 29·3. $C_9H_{12}ON_4$ requires C, 56·3; H, 6·3; N, 29·2%). Similarly prepared were 2 : 6-*diaziridino*-4-*ethoxy*-, b. p. 107°/0·1 mm. (Found : C, 57·8; H, 7·3; N, 26·6. $C_{10}H_{14}ON_4$ requires C, 58·3; H, 6·8; N, 27·2%), and -4-iso*propoxy-pyrimidine*, b. p. 114°/0·05 mm. (Found : N, 26·0. $C_{11}H_{16}ON_4$ requires N, 25·5%).

2 : 4 : 6-*Trichloro*-5-*phenylpyrimidine*.—5-Phenylbarbituric acid (D.R.-P. 247,952; *Frdl.*, **11**, 926) (35 g.) was heated under reflux with phosphoryl chloride (100 c.c.) and dimethylaniline (35 c.c.) for 1 hour, cooled, and poured on ice. The white solid which separated was filtered off and dried in a vacuum over phosphoric oxide. Crystallisation from light petroleum (b. p. 60—80°) gave white needles (23.8 g.) of 2 : 4 : 6-*trichloro*-5-*phenylpyrimidine*, m. p. 160° (Found : C, 46·2; H, 1·75; N, 11·0; Cl, 41·1. $C_{10}H_4N_2Cl_3$ requires C, 46·4; H, 1·5; N, 10·8; Cl, 41·2%).

2 : 6-*Diaziridino*-4-*chloro*-5-*phenylpyrimidine*.—To a solution of ethyleneimine (10 g.) and triethylamine (25 g.) in benzene (200 c.c.) was added 2 : 4 : 6-trichloro-5-phenylpyrimidine (14·6 g.) with stirring at 30—40°. Stirring was continued at 35—40° for 1 hour, the reaction mixture was filtered, and the filtrate evaporated below 40° to a sticky solid. Extraction of this with light petroleum (b. p. 60—80°) yielded, after cooling, a white solid which, crystallised from the same solvent, gave the *diaziridino*-compound (4·0 g.) as needles, m. p. 116—118° (Found : N, 20·2; Cl, 12·8. $C_{14}H_{15}N_4Cl$ requires N, 20·55; Cl, 13·0%).

2-*Aryl*-4 : 6-*dihydroxypyrimidines*.—These compounds were prepared by condensation of ethyl malonate with the appropriate amidine. The following exemplifies the method. Benzamidine hydrochloride (65·2 g.) and ethyl malonate (67 g., 1·1 mols.) were added to a solution of sodium (25·7 g., 3 atoms) in dry ethanol (400 c.c.). After 3 hours' stirring under reflux the solvent was distilled off, the residue taken up in hot water, and the resulting solution acidified with hydrochloric acid. The precipitated 4 : 6-dihydroxy-2-phenylpyrimidine was filtered off, dried at 100°, and recrystallised from aqueous dimethylformamide. It had m. p. 326° (decomp.) (66 g.).

Similarly prepared were : 4 : 6-*dihydroxy*-2-β-*naphthyl*- (98%), m. p. 316—318° (decomp.) (Found : N, 11·2. $C_{14}H_{10}O_2N_2$ requires N, 11·7%), -2-p-*ethoxyphenyl*- (86%), m. p. 289—291° (decomp.) (Found : N, 11·6. $C_{12}H_{12}O_3N_2$ requires N, 12·1%), and -2-p-*tolyl*-*pyrimidine* (91%), m. p. 310° (decomp.) (Found : N, 13·8. $C_{11}H_{10}O_2N_2$ requires N, 13·85%), all crystallised from aqueous dimethylformamide.

Nitrations.—4 : 6-*Dihydroxy*-5-*nitro*-2-*phenylpyrimidine* [With R. Hull]. 4 : 6-Dihydroxy-2-phenylpyrimidine (34 g.) was added to nitric acid (170 c.c.; *d* 1·5) with cooling and stirring at 10—20°. After 15 minutes' stirring at 20° the mixture was poured on ice and the 4 : 6-*dihydroxy*-5-*nitro*-2-*phenylpyrimidine* (29 g., 68%) filtered off, washed with water, and dried (Found : C, 51·3; H, 3·2; N, 18·3. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%). 2-p-Chlorophenyl-4 : 6-dihydroxypyrimidine similarly yielded 2-p-*chlorophenyl*-4 : 6-*dihydroxy*-5-*nitropyrimidine* (49%) as a pale yellow powder (from aqueous dimethylformamide), m. p. 300° (decomp.) (Found : C, 44·5; H, 1·7; Cl, 12·6. $C_{10}H_6O_4N_3Cl$ requires C, 44·9; H, 2·2; Cl, 13·2%). Similar treatment of 4 : 6-dihydroxy-2-*p*-methoxyphenylpyrimidine gave 4 : 6-*dihydroxy*-2-(4-*methoxy*-3-*nitrophenyl*)-5-*nitropyrimidine* (42%), as an orange-yellow powder, m. p. 246—248° (decomp.) (Found : N, 18·3. $C_{11}H_8O_7N_4$ requires N, 18·2%). From 4 : 6-dihydroxy-2-*p*-ethoxyphenylpyrimidine was likewise obtained 2-(4-*ethoxy*-3-*nitrophenyl*)-4 : 6-*dihydroxy*-5-*nitropyrimidine* (42%), m. p. 268—270° (decomp.) (from aqueous dimethylformamide) (Found : C, 45·3; H, 3·5; N, 17·3. $C_{12}H_{10}O_7N_4$ requires C, 44·8; H, 3·1; N, 17·4%).

4 : 6-Dihydroxy-2-β-naphthylpyrimidine (28 g.) was added with stirring to nitric acid (560 c.c.; *d* 1·4) at 20°. Stirring was maintained for 20 minutes, the temperature being allowed to rise to 30—35°. The suspension was then poured into ice-water (3 l.) and filtered. Crystallisation of the crude solid from aqueous dimethylformamide gave 4 : 6-*dihydroxy*-2-β-*naphthyl*-5-*nitropyrimidine* (16·8 g.) as a yellow powder, m. p. 328° (decomp.) (Found : C, 59·7; H, 3·3; N, 15·2. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·9%).

Nitration with nitric acid (*d* 1·5) in the usual manner gave 4 : 6-dihydroxy-2-(*x*-nitro-*p*-tolyl)-5-nitropyrimidine (76%), m. p. 298° (decomp.), which was not obtained analytically pure, although chlorination (see below) yielded a pure dichloro-compound.

4 : 6-Dichloro-2-*p*-ethoxyphenylpyrimidine (3·5 g.) was stirred for 15 minutes with nitric acid (50 c.c.; *d* 1·5) at 20° and then poured on ice. The crude product was filtered off and extracted with boiling light petroleum (b. p. 100—120°). The cooled extracts deposited 4 : 6-*dichloro*-2-(4-*ethoxy*-3-*nitrophenyl*)*pyrimidine* (0·75 g.) which after crystallisation from the same

TABLE 1. *2-Aryl-4 : 6-dichloropyrimidines.*

Aryl	M. p.	Yield, %	Solvent *	Found, % C	H	N	Cl	Formula	Required, % C	H	N	Cl
Ph	96°	77	EtOH	53·1	2·9	11·9	31·1	$C_{10}H_6N_2Cl_2$	53·3	2·7	12·4	31·6
p-MeO·C_6H_4	123—124	67	EtOH	52·0	3·1	11·0	27·2	$C_{11}H_8ON_2Cl_2$	51·8	3·1	11·0	27·8
p-EtO·C_6H_4	98	80	EtOH	54·0	3·6	10·1	26·5	$C_{12}H_{10}ON_2Cl_2$	53·6	3·7	10·4	26·4
β-$C_{10}H_7$	186	58	EtOH	60·6	2·9	9·7	—	$C_{14}H_8N_2Cl_2$	61·1	2·9	10·2	—
5-Nitro-derivatives.												
Ph	168—169	59	Pet	44·5	1·85	15·3	26·1	$C_{10}H_5O_2N_3Cl_2$	44·5	1·85	14·6	26·3
p-C_6H_4Cl †	134—135	40	Pet	40·0	1·4	13·8	34·7	$C_{10}H_4O_2N_3Cl_3$	39·4	1·3	13·4	34·9
4-MeO·C_6H_3·NO_2-3	188—189	53·5	Pet	38·7	2·3	15·9	20·5	$C_{11}H_7O_5N_4Cl_2$	38·3	1·7	16·2	20·6
x-NO_2·C_6H_4Me-*p*	163	61	Pet	40·3	2·0	17·4	21·2	$C_{11}H_6O_4N_4Cl_2$	40·1	1·8	17·0	21·6
4-EtO·C_6H_3·NO_2-3	153—154	53	Pet	—	—	15·2	—	$C_{12}H_8O_5N_4Cl_2$	—	—	15·6	—
β-$C_{10}H_7$	218—219	63	Pet	—	—	13·1	21·4	$C_{14}H_7O_2N_3Cl_2$	—	—	13·1	22·2

* Pet = light petroleum (b. p. 100—120°). † For 2-*p*-chlorophenyl-4 : 6-dihydroxypyrimidine see Moffatt, *J.*, 1950, 1605.

TABLE 2. *Aziridinopyrimidines.*

Substituent* 2	4	5	6	M. p.†	Yield, %	Solvent ‡	Found, % C	H	N	Cl	Formula	Required, % C	H	N	Cl
NH_2	A	NO_2	Me [c]	156° d.	45	M	43·6	4·2	35·9	—	$C_7H_9O_2N_5$	43·1	4·6	35·9	—
A	Me	NO_2	NH_2 [c]	150 d.	45	M	43·3	4·7	35·3	—	$C_7H_9O_2N_5$	43·1	4·6	35·9	—
—	A	NO_2	A [c]	130 d.	69	M	46·4	4·4	—	—	$C_9H_9O_2N_5$	46·4	4·4	—	—
A	A	NO_2 [a]	—	160 d.	46	E	47·0	4·7	—	—	$C_9H_9O_2N_5$	46·4	4·4	—	—
Me	A	NO_2	A [b]	130 d.	62	M	49·0	5·2	31·5	—	$C_8H_{11}O_2N_5$	48·9	5·0	31·7	—
Ph	Cl	—	A	66—67	56	P	61·9	4·1	18·0	15·6	$C_{12}H_{10}N_3Cl$	62·2	4·3	18·1	15·4
(1)	Cl	—	A	169—170	46	P–B	51·2	3·6	19·5	25·7	$C_{12}H_{10}N_4Cl_2$	51·3	3·6	20·0	25·3
p-MeO·C_6H_4	Cl	—	A	132—134	61	E–B	59·9	4·6	16·1	14·0	$C_{13}H_{12}ON_3Cl$	59·7	4·6	16·1	13·7
p-C_6H_4Cl	A	NO_2	A	160 d.	44·5	A	—	—	21·7	10·7	$C_{14}H_{12}O_2N_5Cl$	—	—	22·0	11·2
p-EtO·C_6H_4	Cl	—	A	103—104	66	P	60·9	5·3	—	12·8	$C_{14}H_{14}ON_3Cl$	61·1	5·1	—	12·9
Ph	A	NO_2	A	160 d.	42	E	59·3	4·7	24·6	—	$C_{14}H_{14}O_2N_5$	59·2	4·9	24·7	—
(2)	A	NO_2	A	160 d.	71	A	52·3	4·4	—	—	$C_{15}H_{14}O_4N_6$	52·6	4·1	—	—
(3)	A	NO_2	A	190 d.	78	E	50·1	3·7	—	—	$C_{15}H_{14}O_5N_6$	50·3	3·9	—	—
β-$C_{10}H_7$	Cl	—	A	112—114	84	P	68·4	4·75	15·0	12·8	$C_{16}H_{12}N_3Cl$	68·2	4·3	14·9	12·6
(4)	A	NO_2	A	160 d.	57	E	52·0	4·55	—	—	$C_{16}H_{16}O_5N_6$	51·7	4·3	—	—
β-$C_{10}H_7$	A	NO_2	A	170 d.	41	A	65·3	4·8	—	—	$C_{18}H_{15}O_2N_5$	64·9	4·5	—	—

* A = aziridino; (1) = *p*-chloroanilino; (2) = *x*-nitro-*p*-tolyl; (3) = 4-methoxy-3-nitrophenyl; (4) = 4-ethoxy-3-nitrophenyl.
† Varies with rate of heating; data are for rapid heating; slow heating gives infusible polymers; " d. " = decomp.
‡ M, methanol; E, ethyl acetate; P, light petroleum (b. p. 60—80°); B, benzene; A, acetone.

Prep. of starting materials: [a] Isay, *Ber.*, 1906, **39**, 252; [b] Huber and Hölscher, *Ber.*, 1938, **71**, 87; [c] Boon, Jones, and Ramage, *J.*, 1951, 96.

solvent had m. p. 118° (Found: C, 45·8; H, 2·9; N, 13·05; Cl, 21·9. $C_{12}H_9O_3N_3Cl_2$ requires C, 45·9; H, 2·9; N, 13·35; Cl, 22·6%).

Chlorination.—This was effected by treatment of the appropriate 4 : 6-dihydroxypyrimidine (1 part) with dimethylaniline (1 part) and phosphoryl chloride (5 parts) under reflux for 1 hour. The excess of phosphoryl chloride was distilled off under reduced pressure and the residue triturated with ice; recrystallisation was from ethanol or light petroleum (b. p. 100—120°) as indicated in Table 1 where the properties of the *products* are summarised.

Reaction of Chloropyrimidines with Ethyleneimine.—To a solution of ethyleneimine (2·1 mols.) and triethylamine (2·2 mols.) in dry benzene was added, with stirring and cooling, a solution of the appropriate chloropyrimidine (1·0 mol.) in benzene; or, in the cases of relatively insoluble compounds, the finely ground solid was added; the temperature was kept at 35—45°. Stirring was then continued at this temperature for a further hour, with gentle heating as the exothermic reaction slackened. The mixture was filtered from triethylamine hydrochloride, the filtrate evaporated at >40° under reduced pressure, and the residue recrystallised as indicated in Table 2. A certain amount of the less soluble products was filtered off with the triethylamine hydrochloride and was recovered by leaching the latter with water. In the case of the unnitrated 4 : 6-dichloropyrimidines only one chlorine atom was replaced by this procedure. Both chlorine atoms of compounds having in addition a 5-nitro-group were replaced. The characteristics of the products obtained are summarised in Table 2.

Reaction of 4 : 6-Dichloro-2-phenylpyrimidine with Lithioethyleneimine.—Lithium (1·4 g., 0·2 atom), in small pieces, was stirred in sodium-dried ether (30 c.c.) in an atmosphere of dry nitrogen while methyl iodide (14·2 g., 0·1 mol.) was added in dry ether (30 c.c.) during 0·5 hour. The reaction was moderated as necessary by cooling. Stirring under nitrogen was continued for a further 0·5 hour, by which time the reaction had ceased, although small fragments of lithium remained. Ethyleneimine (3·65 c.c., 0·07 mol.) in dry ether (30 c.c.) was added to the stirred mixture during 0·5 hour, and after a further 0·5 hour's stirring 4 : 6-dichloro-2-phenylpyrimidine (4·5 g., 0·02 mol.) in ether (50 c.c.) was added with gentle boiling. Refluxing was continued for a further hour, the solution then filtered from residual lithium through 100-mesh gauze, and the filtrate decomposed with ice and water (100 c.c.). The ethereal layer was separated and the aqueous layer twice extracted with further quantities of ether. The combined extracts were dried (Na_2SO_4) and evaporated, to yield crude 4 : 6-*diaziridino-2-phenylpyrimidine* which recrystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 111—112° (1·8 g., 38%) (Found: C, 70·0; H, 6·15; N, 23·35. $C_{14}H_{14}N_4$ requires C, 70·6; H, 5·9; N, 23·5%). Similarly prepared was 4 : 6-*diaziridino-2-β-naphthylpyrimidine* (41%), m. p. 156—158° with polymerisation (Found: C, 14·6; H, 5·4; N, 19·7. $C_{18}H_{16}N_4$ requires C, 75·0; H, 5·6; N, 19·4%).

5-Amino-4 : 6-diaziridino-2-phenylpyrimidine.—4 : 6-Diaziridino-5-nitro-2-phenylpyrimidine (3·0 g.) in benzene (40 c.c.)–methanol (40 c.c.) was shaken with hydrogen over Raney nickel. Uptake was 723 c.c. (theor., 765 c.c. at 20°); the reaction mixture was filtered and evaporated below 40° to a red solid which was recrystallised repeatedly from acetone (carbon) and yielded 5-*amino*-4 : 6-*diaziridino*-3-*phenylpyrimidine* (0·8 g.) as a pale yellow microcrystalline powder, m. p. 147—148° (Found: N, 27·4. $C_{14}H_{15}N_5$ requires N, 27·7%).

Oxidation of 4 : 6-Dihydroxy-2-(4-methoxy-3-nitrophenyl)-5-nitropyrimidine.—The pyrimidine (5 g.) was dissolved in a solution of sodium hydroxide (1·3 g., 2·0 mols.) in hot water (100 c.c.), and hot 10% aqueous potassium permanganate was added at 80° during 0·5 hour. When about 120 c.c. had been added a permanent purple colour resulted; the reaction mixture was kept at 80° for a further 45 minutes and filtered hot from manganese salts. The filtrate was acidified with sulphuric acid and crude 4-methoxy-3-nitrobenzoic acid separated. The crude acid (0·92 g.), after several crystallisations from aqueous methanol, had m. p. 185—186° alone or mixed with an authentic sample. The product was further characterised as the methyl ester, m. p. 108°. Similar oxidation of 4 : 6-dihydroxy-5-nitro-2-phenylpyrimidine yielded benzoic acid identified by m. p. and mixed m. p.

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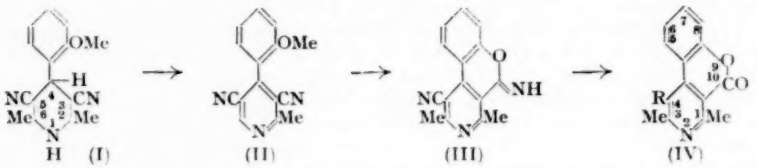
69. *New Syntheses of Heterocyclic Compounds. Part XV.** 9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrenes.*

By A. Courts and V. Petrow.

A new extension of the Hantzsch–Meyer–Mohr group of pyridine syntheses is reported whereby certain derivatives of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene may be obtained. The limitations of the method are indicated and the nitration of the parent ring system is described.

Reduced forms of the 9 : 10-dihydro-2-aza-9-oxaphenanthrene ring system,† which bear a formal resemblance to the psychogenic drugs of the cannabinol group, have formed the object of study. Work on the fully aromatic nucleus, in contrast, appears to be



confined to the observations of Kahn, Petrow, Rewald, and Sturgeon (*J.*, 1949, 2128), who obtained (IV; R = H) while attempting ring closure of 4-*o*-methoxyphenyl-2 : 6-dimethylpyridine-3-carboxylic acid to the corresponding methoxy-2-azafluorenone. We have, therefore, carried out some preparative experiments in this field, and now report a novel synthesis whereby certain derivatives of (IV) may be obtained.

Condensation of *o*-methoxybenzaldehyde with 2 mols. of β-aminocrotononitrile in glacial acetic acid (cf. Part XIII, *loc. cit.*) led to the formation of 3 : 5-dicyano-1 : 4-dihydro-4-*o*-methoxyphenyl-2 : 6-dimethylpyridine (I) in nearly quantitative yield. Oxidation of this with chromium trioxide furnished the corresponding pyridine derivative (II). The latter, on being heated with 48% hydrobromic acid, in which it is freely soluble, passed smoothly into 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene (IV; R = CN), presumably by way of the intermediate (III). By employing β-aminocinnamonitrile in the synthesis, 4-cyano-9 : 10-dihydro-10-keto-1 : 3-diphenyl-2-aza-9-oxaphenanthrene was likewise obtained in excellent overall yield. Hydrolysis to the corresponding 4-carboxylic acids, however, could not be effected, the nitriles being recovered unchanged after even 8 hours' refluxing with concentrated hydrobromic acid.

Mononitration was readily effected by heating (IV; R = CN) with fuming nitric acid on the water-bath. The product, obtained in nearly quantitative yield, was assigned the constitution of 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene (see below). In marked contrast to the un-nitrated compound (IV; R = CN), treatment with boiling hydrobromic acid led to hydrolysis of the cyano-group with formation of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene-4-carboxylic acid, characterised as its ethyl ester. The structure of this compound was rigidly confirmed by its alternative synthesis from 2-methoxy-5-nitrobenzaldehyde and β-aminocrotonitrile. Its decarboxylation, which occurred with explosive facility, furnished 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene in low yield, identical with the product obtained by direct nitration of (IV; R = H), the constitution of which is accordingly established.

The foregoing nitro-derivatives retained the characteristic property of nitrophenols in being freely soluble in alkali with production of intensely yellow salts formed, no doubt, by

* Part XIV, *J.*, 1952, 228.

† *Note on nomenclature :* In view of the structural similarity between (IV) and the diazaphenanthrenes described in Parts V, VII, and XIII of this series (Petrow, *J.*, 1946, 200, 884; Courts and Petrow, *J.*, 1952, 1), the nomenclature of (IV) is based on phenanthrene and not on pyridinocoumarin.

rupture of the 9 : 10-lactone bridge, which was reconstituted on acidification. Reduction of 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene, and of its 4-cyano-derivative with reduced iron in acidulated ethanol gave the corresponding amines in good yield.

Only a limited range of compounds proved capable of synthesis by this route. 2 : 4-Dimethoxybenzaldehyde behaved in the expected manner, furnishing 3 : 5-dicyano-4-(2 : 4-dimethoxyphenyl)-2 : 6-dimethylpyridine after oxidation. Short treatment of this compound with hydrobromic acid gave 4-cyano-9 : 10-dihydro-10-keto-7-methoxy-1 : 3-dimethyl-2-aza-9-oxaphenanthrene, the corresponding 7-hydroxy-compound being obtained if contact with the hydrolytic agent was prolonged beyond 30 minutes. The pyridine derivatives derived from 2 : 4-dimethoxy-5-nitro- and 2 : 5-dimethoxy-6-nitrobenzaldehyde, however, failed to yield oxazaphenanthrenes on treatment with hydrobromic acid, unidentified products being obtained. 2-Methoxy-1-naphthaldehyde did not appear to react with β-aminocrotononitrile, an unexpected result as the unsubstituted aldehyde behaves normally in the Hantzsch condensation (Kahn, Petrow, Rewald, and Sturgeon, *loc. cit.*). Attempts to prepare (IV; R = COMe) also proved unsuccessful. *o*-Methoxybenzaldehyde failed to condense with acetylacetone (cf. Part XIII; Courts and Petrow, *loc. cit.*). Somewhat better results were obtained employing 2-methoxy-5-nitrobenzaldehyde, which gave 3-(2-methoxy-5-nitrobenzylidene)pentane-2 : 4-dione in 73% yield. Reaction with β-aminocrotononitrile, followed by oxidation gave 5-acetyl-3-cyano-4-(2-methoxy-5-nitrophenyl)-2 : 6-dimethylpyridine, but ring closure of this compound to the corresponding azaoxaphenanthrene could not be accomplished.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss.

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-*o*-*methoxyphenyl*-2 : 6-*dimethylpyridine* (I), prepared by heating *o*-methoxybenzaldehyde (4 g.), β-aminocrotononitrile (5·25 g.), and glacial acetic acid (25 ml.) under reflux for 1 hour, formed prismatic needles, m. p. 190°, from acetic acid–light petroleum (Found : C, 72·2; H, 5·6; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·8%).

3 : 5-*Dicyano*-4-*o*-*methoxyphenyl*-2 : 6-*dimethylpyridine* (II), large pale yellow plates (74%) (from glacial acetic acid), m. p. 177° (Found : C, 73·0; H, 4·7; N, 15·8. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%), was obtained by oxidising the foregoing compound (5 g.) in hot glacial acetic acid (15 ml.) with chromium trioxide (1·5 g.) added dropwise in aqueous solution.

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene* (IV; R = CN) separated (82%) when the foregoing compound (9 g.) was heated with 48% hydrobromic acid (60 ml.) under reflux for 2 hours. It formed light brown needles, m. p. 281°, from glacial acetic acid (Found : C, 71·9; H, 3·9; N, 11·0. $C_{15}H_{10}O_2N_2$ requires C, 71·7; H, 4·0; N, 11·2%).

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-*o*-*methoxyphenyl*-2 : 6-*diphenylpyridine*, obtained in nearly quantitative yield by gently heating *o*-methoxybenzaldehyde (2·25 g.), β-aminocinnamonitrile (5 g.), and glacial acetic acid (15 ml.) under reflux for 20 minutes, formed lemon-yellow prisms (from ethanol), m. p. 242·5° (Found : C, 80·2; H, 5·0; N, 10·7. $C_{26}H_{19}ON_3$ requires C, 80·2; H, 4·9; N, 10·8%).

3 : 5-*Dicyano*-4-*o*-*methoxyphenyl*-2 : 6-*diphenylpyridine*, obtained (80%) by treating a hot suspension of the foregoing compound (5 g.) in glacial acetic acid (30 ml.) with chromium trioxide (1·5 g.) dissolved in a little water, separated from a large volume of glacial acetic acid in faintly yellow needles, m. p. 219—220° (Found : C, 80·7; H, 4·3; N, 11·0. $C_{26}H_{17}ON_3$ requires C, 80·6; H, 4·4; N, 10·8%).

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*diphenyl*-2-*aza*-9-*oxaphenanthrene* was obtained (40%) by heating the foregoing dinitrile (250 mg.) with 48% hydrobromic acid (100 ml.) for 3 hours under reflux, most of the solid dissolving. After cooling, the mixture was filtered through sintered glass and poured into water (150 ml.), and the precipitated solids were crystallised from glacial acetic acid, whereupon feathery needles were obtained, having m. p. 299° (Found : C, 79·9; H, 3·4; N, 7·2. $C_{25}H_{14}O_2N_2$ requires C, 80·2; H, 3·7; N, 7·5%).

4-*Cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*, obtained by warming a solution of (IV; R = CN) (1 g.) in fuming nitric acid (5 ml.) for 7—8 minutes on the water-bath, followed by precipitation on to crushed ice, formed flat needles (from ethanol),

m. p. 191° (Found : C, 60·7; H, 2·8; N, 13·9. $C_{15}H_9O_4N_3$ requires C, 61·0; H, 3·0; N, 14·2%). An aqueous solution of the compound gave a transient red colour with 1 drop of ferric chloride solution.

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine*, obtained in nearly quantitative yield by heating 2-methoxy-5-nitrobenzaldehyde (4·5 g.), β-aminocrotononitrile (4 g.), and glacial acetic acid (20 ml.) under reflux for 15 minutes, formed needles, m. p. 226—229°, from absolute ethanol (Found : C, 62·0; H, 4·4; N, 18·1. $C_{16}H_{14}O_3N_4$ requires C, 61·9; H, 4·5; N, 18·1%).

3 : 5-*Dicyano*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine* formed pale yellow needles (90%), m. p. 222·5—223°, from ethanol (Found : C, 62·4; H, 4·0; N, 18·4. $C_{16}H_{12}O_3N_4$ requires C, 62·3; H, 3·9; N, 18·2%).

9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*-4-*carboxylic Acid*.—(i) The foregoing compound (4 g.) was heated under reflux with 48% hydrobromic acid (40 ml.) for 8 hours, the solution was poured on ice, and the precipitated solids were crystallised from 100 vols. of glacial acetic acid. The *acid* (25%) formed small dark yellow crystals, m. p. 264° (vigorous decomp.) (Found : C, 56·8; H, 3·4; N, 8·6. $C_{15}H_{10}O_6N_2$ requires C, 57·3; H, 3·2; N, 8·9%).

(ii) When 4-cyano-9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene (200 mg.) was heated with 48% hydrobromic acid (3 ml.) under reflux for 2 hours, and the solution poured on crushed ice, 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene-4-carboxylic acid was obtained, m. p. 264°, alone or on admixture with a sample prepared by method (i).

The acid (1 g.), suspended in absolute ethanol (200 ml.), was treated with a stream of dry hydrogen chloride (*ca.* 8 g.), the material passing into solution. After 8 hours' heating under reflux the bulk of the solvent was removed by distillation, and water (50 ml.) added. After addition of dilute aqueous ammonia until faintly acid, the mixture was set aside overnight; then the precipitated solids were collected and crystallised from benzene. The *ethyl* ester formed pale yellow plates (68%), m. p. 159—160° (Found : N, 8·0. $C_{17}H_{14}O_6N_2$ requires N, 8·2%).

9 : 10-*Dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene*.—(i) 9 : 10-Dihydro-10-keto-1 : 3-dimethyl-2-aza-9-oxaphenanthrene (IV; R = H) was prepared by the following improved procedure (cf. Kahn *et al.*, *loc. cit.*) : 4-*o*-Methoxyphenyl-2 : 6-dimethylpyridine-3-carboxylic acid hydrogen sulphate (10 g.) was cautiously treated with thionyl chloride (50 ml.). When the initial reaction had subsided the mixture was heated under reflux for 10 minutes. After removal of excess of thionyl chloride under reduced pressure, dilute aqueous ammonia was added until the mixture was just alkaline to litmus, and the precipitated solids were collected and crystallised from benzene, giving (IV; R = H), m. p. 203° (Found : N, 6·3. Calc. for $C_{14}H_{11}O_2N$: N, 6·2%) alone or on admixture with an authentic specimen.

The foregoing compound (250 mg.), dissolved in fuming nitric acid (5 ml.), was heated on the water-bath for 2 hours. The mixture was then poured into water (10 ml.). The precipitated solids, on crystallisation from alcohol, gave 9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-6-*nitro*-2-*aza*-9-*oxaphenanthrene* (73%), small needles, m. p. 241° (Found : C, 62·1; H, 3·7; N, 10·4. $C_{14}H_{10}O_4N_2$ requires C, 62·2; H, 3·7; N, 10·4%).

(ii) When the 6-nitro-derivative of (IV; R = CO_2H) (see above) was cautiously heated above its m. p., 9 : 10-dihydro-10-keto-1 : 3-dimethyl-6-nitro-2-aza-9-oxaphenanthrene was obtained, having m. p. 241° alone or on admixture with a sample prepared by method (i).

6-*Amino*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene*, obtained in nearly quantitative yield by heating the foregoing nitro-compound (30 mg.) in ethanol (20 ml.) containing 1 drop of concentrated hydrochloric acid with reduced iron (100 mg.) under reflux for 20 minutes and then concentrating the filtrate until crystallisation commenced, formed feathery yellow needles (from ethanol), m. p. 281·5° (decomp.) (Found : C, 69·9; H, 5·0; N, 11·6. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%).

The *acetyl* derivative formed needles (84%) (from chloroform), m. p. 286·5—287° (Found : C, 67·6; H, 5·0. $C_{16}H_{14}O_3N_2$ requires C, 68·0; H, 5·0%).

6-*Amino*-4-*cyano*-9 : 10-*dihydro*-10-*keto*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene*, prepared by reduction of the corresponding nitro-compound (500 mg.) in ethanol (50 ml.) containing 2 drops of concentrated hydrochloric acid with reduced iron (1·5 g.) under reflux for 40 minutes, separated from the filtrate on cooling in lemon-yellow needles (62%), m. p. >310° (Found : C, 67·4; H, 4·2; N, 15·5. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·8%). The compound diazotises and couples with alkaline β-naphthol in the usual manner.

3 : 5-*Dicyano*-1 : 4-*dihydro*-4-(2 : 4-*dimethoxyphenyl*)-2 : 6-*dimethylpyridine* formed needles (80%), m. p. 210—211°, from absolute ethanol (Found : C, 69·4; H, 5·8; N, 14·0. $C_{17}H_{17}O_2N_3$ requires C, 69·2; H, 5·8; N, 14·2%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxyphenyl*)-2 : 6-*dimethylpyridine* was obtained in nearly quantitative yield as lustrous flat yellow needles, m. p. 134·5°, from absolute ethanol (Found : C, 69·8; H, 5·2; N, 14·3. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%).

4-*Cyano*-9 : 10-*dihydro*-7-*methoxy*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene*, obtained by heating the foregoing compound (3·5 g.) with 48% hydrobromic acid for 30 minutes, formed small needles, m. p. 236°, from absolute ethanol (Found : C, 68·1; H, 4·3; N, 10·2; OMe, 12·7. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0; OMe, 11·1%).

Hydrolysis for a further 4 hours furnished **4-*cyano*-9 : 10-*dihydro*-7-*hydroxy*-1 : 3-*dimethyl*-2-*aza*-9-*oxaphenanthrene hemihydrate***, buff spear-shaped needles, m. p. 271—273° (decomp.), from ethanol containing a few drops of ammonia (Found : C, 65·9; H, 4·1; N, 10·0. $C_{15}H_{10}O_3N_2,\frac{1}{2}H_2O$ requires C, 65·5; H, 4·0; N, 10·2%).

The *acetyl* derivative formed light brown needles (from aqueous acetic acid), m. p. 201° (Found : C, 66·1; H, 4·0; N, 9·0. $C_{17}H_{12}O_4N_2$ requires C, 66·2; H, 3·9; N, 9·1%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxy*-5-*nitrophenyl*)-1 : 4-*dihydro*-2 : 6-*dimethylpyridine* formed faintly yellow tetragonal prisms (80%) from absolute ethanol and had m. p. 192—193° (dried at 120° for 24 hours) (Found : C, 60·4; H, 4·8; N, 16·5. $C_{17}H_{14}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

3 : 5-*Dicyano*-4-(2 : 4-*dimethoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine* formed faintly yellow prismatic needles (90%), m. p. 229°, from ethanol (Found : C, 60·9; H, 4·3; N, 16·6. $C_{17}H_{14}O_4N_4$ requires C, 60·4; H, 4·1; N, 16·6%).

3 : 5-*Dicyano*-4-(2 : 5-*dimethoxy*-6-*nitrophenyl*)-1 : 4-*dihydro*-2 : 6-*dimethylpyridine* formed small lemon-yellow needles (62%) (from ethanol), m. p. 268—273° (decomp.) (Found : C, 60·0; H, 4·7; N, 16·6. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%).

3 : 5-*Dicyano*-4-(2 : 5-*dimethoxy*-6-*nitrophenyl*)-2 : 6-*dimethylpyridine* was obtained in flat, pale yellow needles (90%), m. p. 229—229·5°, from ethanol (Found : C, 60·4; H, 4·0; N, 16·3. $C_{17}H_{14}O_4N_4$ requires C, 60·4; H, 4·1; N, 16·6%).

3-(2-*Methoxy*-5-*nitrobenzylidene*)*pentane*-2 : 4-*dione*, prepared by dissolving finely powdered 2-methoxy-5-nitrobenzaldehyde (3 g.) in acetylacetone, adding 5 drops of piperidine, and leaving the mixture for 4 hours in a vacuum-desiccator, formed large flat needles (73%), m. p. 122—122·5°, from ethanol (Found : C, 59·5; H, 5·0; N, 5·3. $C_{13}H_{13}O_5N$ requires C, 59·3; H, 4·9; N, 5·3%).

5-*Acetyl*-3-*cyano*-1 : 4-*dihydro*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine*, prepared by fusing the foregoing compound (1·1 g.) with β-aminocrotononitrile (300 mg.), separated from absolute ethanol in yellow needles (71%), m. p. 211—211·5° (Found : C, 62·4; H, 5·3; N, 12·6. $C_{17}H_{17}O_4N_3$ requires C, 62·4; H, 5·2; N, 12·8%).

5-*Acetyl*-3-*cyano*-4-(2-*methoxy*-5-*nitrophenyl*)-2 : 6-*dimethylpyridine* formed small needles (88%), m. p. 166°, from ethanol (Found : C, 62·4; H, 4·7; N, 13·1. $C_{17}H_{15}O_4N_3$ requires C, 62·8; H, 4·6; N, 12·9%).

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70. *The Ultra-violet Absorption Spectra of Sodium Hyponitrite and Sodium α-Oxyhyponitrite: the Analysis of Mixtures with Sodium Nitrite and Nitrate.*

By C. C. Addison, G. A. Gamlen, and R. Thompson.

The ultra-violet absorption spectra of sodium hyponitrite ($Na_2N_2O_2$) and sodium α-oxyhyponitrite ($Na_2N_2O_3$) in alkaline solution have been redetermined, over the range 230—370 mμ. (The α and β nomenclature for these compounds is defined.) Sodium hyponitrite shows one peak at 248 mμ, log $\varepsilon_{max.} = 3{\cdot}60$; sodium α-oxyhyponitrite gives an absorption curve of similar shape, with one peak at the same wave-length and log $\varepsilon_{max.} = 3{\cdot}92$. Absorption-spectra measurements have been applied to the analysis of mixtures of these ions with nitrate and nitrite. Modes of decomposition in alkaline solution have been studied; solutions of sodium hyponitrite, on long storage at room temperature, decompose to give solutions containing only sodium hydroxide, whilst sodium α-oxyhyponitrite is quantitatively oxidised to nitrite by atmospheric oxygen according to the equation $Na_2N_2O_3 + O = 2NaNO_2$. The structures of the hyponitrite and α-oxyhyponitrite ions are discussed.

Reactions of liquid dinitrogen tetroxide with sodium hyponitrite ($Na_2N_2O_2$) and sodium α-oxyhyponitrite ($Na_2N_2O_3$) are discussed in the following paper. The products of these reactions when dissolved in water give solutions which may contain hydroxide, nitrite, and nitrate together with the more complex oxyacid ions, and chemical methods of analysis for a particular ion are subject to appreciable interference from the other ions present. For example, hyponitrite alone in aqueous solution may be determined by direct titration with strong mineral acids (Oza, Dipali, and Oza, *J. Indian Chem. Soc.*, 1950, **27**, 409). This method cannot be employed in the presence of hydroxide, and owing to the decomposition of the indicator, the end-point is not sharp in the presence of nitrite. Nitrite again interferes with the determination of hyponitrite by means of potassium permanganate (see Partington and Shah, *J.*, 1931, 2071). Since the hyponitrite ion is less stable in solution than the nitrite ion, the difficulties involved in the chemical determination of nitrite in the presence of hyponitrite are even greater. In view of the possible interconversion of certain of these ions in solution, and the instability of solutions of sodium hyponitrite and α-oxyhyponitrite, it was clear that a rapid physical method was preferable for both the identification of the ions and their determination. The most suitable method was considered to be that of ultra-violet spectrophotometric analysis, and some of the conclusions in the following paper are based upon this form of analysis of reaction products. However, before such analyses could be carried out it was necessary to establish accurate values for the absorption of the oxyacid ions, both singly and in mixtures. Results of this preliminary work are considered in the present paper.

Nomenclature.—By the accepted use of the prefix hypo-, the name hyponitrous acid should be applied to the unknown acid HNO. However, this name has now been widely accepted for the acid $H_2N_2O_2$ and has been approved in the I.U.P.A.C. Rules.

The name hyponitric acid has been applied to the compound $H_2N_2O_3$ by each of the authors to whom reference is made in this paper. There appears to be no justification for this and, since the chemistry of salts of this acid has been studied less extensively than those of hyponitrous acid, the use of the name hyponitric acid should be discontinued. The name oxyhyponitrous acid is preferred, at least until the structure of the acid is known with certainty.

The salt $Na_2N_2O_3$ occurs in two forms. The compound prepared from hydroxylamine and ethyl nitrate will be termed sodium α-oxyhyponitrite, and only this form of the compound is considered in the present paper. The compound obtained by oxidation of sodium hyponitrite with dinitrogen tetroxide (described in the following paper) will be termed sodium β-oxyhyponitrite.

Sodium Hyponitrite.—Baly and Desch (*J.*, 1908, **93**, 1747) first determined the ultra-violet absorption spectrum for aqueous solutions of sodium hyponitrite (without added

alkali) over a limited wave-length range which did not include the peak of the curve. Their measurements were not expressed in modern terminology, and the curve is difficult to interpret quantitatively. Kortum and Finckh (*Z. physikal. Chem.*, 1941, *B*, **48**, 42), using a photographic method, obtained the values shown as curve *C*, Fig. 1, for a solution in 0·1N-sodium hydroxide. The curve passes through a maximum and log $\varepsilon_{max.} = 3{\cdot}54$. The present measurements (curve *A*, Fig. 1) confirm the general shape and position of Kortum and Finckh's curve; we find the curve to pass through a maximum at a similar wave-length (248 mμ) but curve *A* is displaced slightly towards higher ε values, with log $\varepsilon_{max.} = 3{\cdot}60$. The measurements recorded on curve *A* were completed within one hour of preparation of the solution. Identical ε values were obtained for solutions in N- and in 0·1N-sodium hydroxide, so that 0·1N-sodium hydroxide is adequate to prevent detectable

FIG. 1.

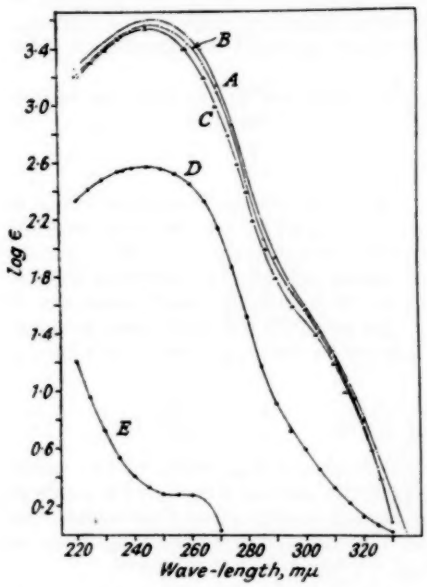
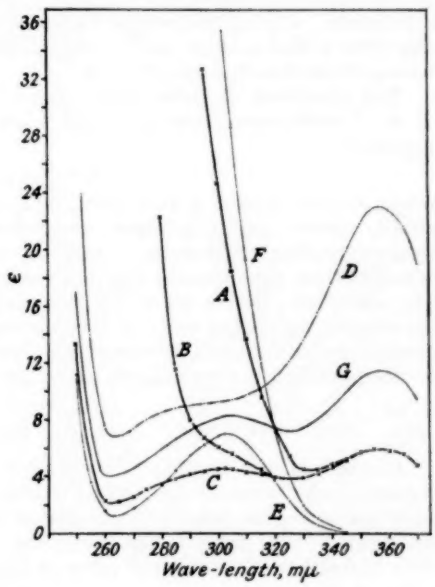


FIG. 2.



hydrolysis during the time required for determination of the spectrum. Abel and Proisl (*Monatsh.*, 1938, **72**, 1) studied the decomposition of sodium hyponitrite solutions by titration with potassium permanganate solution, and observed that the rates of decomposition, at 25° and above, varied considerably with the alkalinity of the solution. The same effect is illustrated in Fig. 1. A solution of sodium hyponitrite in N-sodium hydroxide was kept in the dark at about 20° for 9 days, and curve B was then obtained. Under these conditions only slight decomposition occurs; comparison of the $\varepsilon_{max.}$ values showed that about 90% of the hyponitrite still remained. A similar experiment, employing 0·1N-sodium hydroxide, gave curve *D*, and the $\varepsilon_{max.}$ value shows that only 9% of the hyponitrite remained. It is of interest that after 10 weeks in 0·1N-sodium hydroxide (curve *E*), the presence of a trace of hyponitrite is still detectable in the ultra-violet spectrum of the solution, although this is not detectable by chemical methods.

Analysis of Hyponitrite–Nitrite–Nitrate Mixtures.—Curve *A* (Fig. 2) is a portion of the absorption curve on a linear scale, obtained for the mixture, in 0·1N-sodium hydroxide, when the components are present in the ratio 2 : 1 : 1. This mixture was selected since it is typical of the products of reaction between sodium hyponitrite and liquid dinitrogen tetroxide (following paper). Beer's law is obeyed by this system, since curve *A* is identical with that constructed from the separate absorption curves for the pure constituents. The curves for pure sodium nitrite and sodium nitrate (obtained from solutions of the

"AnalaR" oven-dried salts) and the relevant portion of the sodium hyponitrite curve (*D*, *E*, and *F*, respectively) are superimposed in Fig. 2. The nitrite peak was obtained at 357 mμ, and $\varepsilon_{max.} = 23{\cdot}0$, compared with Kortum's value of 21·9 (*Z. physikal. Chem.*, 1939, *B*, **43**, 421). The nitrate curve shows a peak at 302·5 mμ, $\varepsilon_{max.} = 7{\cdot}01$, compared with 7·2 (Kortum and Finckh, *loc. cit.*), and the value 7·06 deduced from the mean value of *E* (1%, 1 cm.) obtained in a collaborative test on aqueous potassium nitrate (Photoelectric Spectrometry Group, Bull. 1, 1949).

It is convenient, for analytical purposes, that the absorption of both nitrate and hyponitrite are negligible at the wave-length corresponding to the nitrite peak, and the ε value for the composite curve (*A*) at sufficiently high wave-lengths may be used directly for the estimation of nitrite. Since the peak wave-length for nitrite (357 mμ) is only slightly above the wave-length at which nitrate and hyponitrite become inappreciable, it was considered advisable to employ a somewhat higher wave-length for purposes of estimation. During this work ε values have been determined, and compared, at 365 mμ; this gives a high ε value (21·7) for pure nitrite (curve *D*) without the possibility of interference from the other components.

The estimation of nitrate and hyponitrite may be carried out in two ways, as follows.

(a) *Simultaneous-equation method.* The standard method involves the use of the equation

$$d_\lambda = \varepsilon_1 C_1 + \varepsilon_2 C_2 + \varepsilon_3 C_3$$

where *d* is the optical density ($\log_{10} I_0/I$), C_1, C_2, and C_3 are the molar concentrations of nitrite, nitrate, and hyponitrite respectively, and ε_1, ε_2, and ε_3 are the corresponding molar extinction coefficients. Since C_1 can be determined directly, C_2 and C_3 can be obtained from simultaneous equations obtained by taking *d* values for two wave-lengths. The choice of suitable wave-lengths is influenced by the relatively small absorption of the nitrate, compared with the hyponitrite, ion; 305 and 320 mμ have been found in practice to be convenient wave-lengths, and the following ε values are considered here to be standard for the wave-lengths concerned.

λ, mμ	ε_1	ε_2	ε_3	λ, mμ	ε_1	ε_2	ε_3	λ, mμ	ε_1	ε_2	ε_3
305	9·43	6·95	28·6	320	11·1	3·67	7·10	365	21·7	—	—

In view of the method of calculation involved, and the magnitude of the above constants, the accuracy with which nitrate or hyponitrite can be determined depends to some extent on the relative quantities of the ions present as well as on their actual concentrations. The table below shows the calculated percentage error resulting from an error of 0·001 in the measured value of $(d_{305} - d_{320})$, for three typical mixtures.

Mol. ratio $N_2O_2^{2-} : NO_2^- : NO_3^-$	$d_{305} - d_{320}$	Error, %, in determination of: $Na_2N_2O_2$	$NaNO_3$
2 : 1 : 1	0·180	0·8	3·4
1 : 1 : 1	0·093	1·6	3·4
1 : 1 : 2	0·106	1·6	1·7

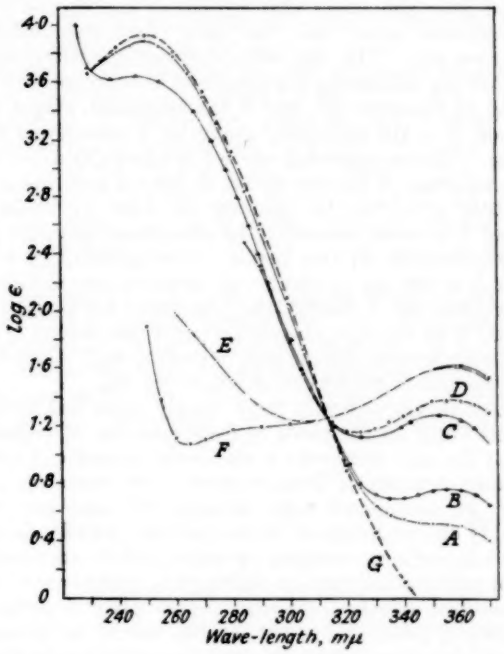
The above errors are calculated on the assumption that no error is involved in the original determination of nitrite; in fact, nitrite may be determined with an accuracy of about 1%, but this has no significant influence on the above figures.

(b) *Removal of hyponitrite.* Solutions of sodium hyponitrite decompose on long storage, or more rapidly on boiling, according to the equation $Na_2N_2O_2 + H_2O = 2NaOH + N_2O$. Since the only decomposition product remaining in the system is sodium hydroxide, which is already present in excess, the removal of hyponitrite provides an alternative, and more accurate, method of analysis. After 9 days in the dark at about 20°, the absorption curve for the 2 : 1 : 1 mixture (originally curve *A*) changed to curve *B* (Fig. 2); curve *C* was obtained after twelve weeks. Curve *G* is the absorption curve derived for an equimolecular mixture of nitrate and nitrite; the curve obtained on complete removal of hyponitrite (curve *C*) will have an ε scale which is half that of curve *G* (since in a 2 : 1 : 1 mixture the original molar concentration used in the calculation of ε from *d* is twice that used for computing curve *G*) but, when allowance is made for this, curves *C* and *G* are identical.

For any mixture, *e.g.*, that corresponding to curve *A*, the nitrite content may be determined directly from d_{365}, as before. The value of *d* at 305 mμ is determined before and after the decomposition of the hyponitrite, and the concentration of hyponitrite is available directly from the change in *d*. The value of d_{305} given by curve *C* then represents the total absorption due to nitrate and nitrite. Knowing d_{365} for nitrite, we can calculate the value of d_{305} for nitrite by proportion from curve *D*, and *d* for nitrate can be obtained by difference.

Sodium α-oxyhyponitrite. Curve *A* (Fig. 3) represents the absorption of sodium α-oxyhyponitrite ($Na_2N_2O_3$) when dissolved in 0·1N-sodium hydroxide. The only measurements on such solutions reported in the literature are those of Kortum and Finckh (*loc. cit.*), whose curve is shown in Fig. 3 as curve *C*. There is a considerable discrepancy

FIG. 3.



between the two curves, particularly in the pronounced peak through which Kortum and Finckh's values pass at 357 mμ. It was necessary in the present work to determine the true absorption curve for sodium α-oxyhyponitrite for two reasons: first, a knowledge of the true curve is essential for the qualitative and quantitative analysis of products of reaction with dinitrogen tetroxide; secondly, a peak in an absorption curve at 357 mμ is characteristic of the nitrite group, and its presence would have an important bearing on the structure of the α-oxyhyponitrite ion, which is still in doubt.

When the fresh solution (curve *A*) was kept in a stoppered vessel at room temperature and absorption curves were redetermined after 11 days and 12 weeks, curves *D* and *E*, respectively, were obtained. Aqueous solutions of sodium α-oxyhyponitrite are known to give nitrite on decomposition (Naik, Shah, and Patel, *J. Indian Chem. Soc.*, 1946, **23**, 284), and the increase in $\varepsilon_{max.}$ at 357 mμ with time was consistent with the progressive decomposition of the solution. It then appeared possible that the flat portion of curve *A* might not be a characteristic of the α-oxyhyponitrite ion but be due to a submerged maximum arising from the presence of nitrite in the original solution. However, chemical analysis (for both sodium and nitrogen content) had shown that the solid sodium α-oxy-

hyponitrite was pure; any nitrite present therefore must be formed during or after the preparation of the fresh solution. This could occur by the decomposition:

$$2Na_2N_2O_3 + H_2O = 2NaNO_2 + 2NaOH + N_2O \quad . \; . \; . \quad (1)$$

(Naik, Shah, and Patel, *loc. cit.*) or by the more rapid atmospheric oxidation noted by Angeli and Angelico (*Gazzetta*, 1900, **30**, 593):

$$Na_2N_2O_3 + O = 2NaNO_2 \quad . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

The presence of any appreciable quantity of nitrite in the fresh solution favours reaction (2); this reaction would also be expected to lead to lack of reproducibility of the absorption curve, since ready atmospheric oxidation is difficult to control. A second determination, carried out under experimental conditions as nearly identical as possible with those employed for curve *A*, gave curve *B*; comparison shows that the curves are not reproducible. It appeared from the above that neither of the curves *A* or *C* was the true α-oxyhyponitrite absorption curve, but that each curve was obtained from solutions containing the nitrite ion also. This has been confirmed quantitatively as follows.

If it is assumed that the decomposition of sodium α-oxyhyponitrite in alkaline solution takes place according to equation (2), and if the molecular weight of sodium nitrite is used in the calculation of ε, the calculated curve for a completely decomposed solution is shown by *F* (Fig. 3). The experimental curve *E* is almost identical with *F* at the higher wave-lengths, and comparison of the two values at 365 mμ indicates a 99% decomposition of the α-oxyhyponitrite according to equation (2) after 12 weeks. The discrepancy between curves *E* and *F* at lower wave-lengths arises from the high extinction values of the remaining α-oxyhyponitrite in this region. The quantity of α-oxyhyponitrite was calculated from curve *E* at 260 mμ, at which ε for nitrite is near the minimum. Allowance being made for absorption due to nitrite, the apparent ε for α-oxyhyponitrite is 84; the value of ε interpolated from the true absorption curve (see below) is 6500, from which it follows that 1·3% of α-oxyhyponitrite remains undecomposed. This is in good agreement with the 99% decomposition to nitrite calculated at 365 mμ.

The present measurements indicate, more clearly than has hitherto been possible, the influence of added alkali on the mode of decomposition of sodium α-oxyhyponitrite. Naik, Shah, and Patel (*loc. cit.*) observed the stabilising influence of added alkalis, without reference to any change in mode of decomposition. In neutral or dilute acid solution, decomposition occurs in accordance with equation (1), and one molecule of sodium α-oxyhyponitrite yields one molecule of sodium nitrite (Angeli, *Gazzetta*, 1896, **26**, 17). However, in alkaline solution two molecules of sodium nitrite are produced [equation (2)]. The same influence of added alkali may be observed in oxidations by means of potassium permanganate. In neutral solution, oxidation takes place according to the equation $Na_2N_2O_3 + 3O = 2NaNO_3$ (*idem*, *ibid.*, 1904, **34**, 50), but in the presence of alkali (Naik, Shah, and Patel, *loc. cit.*) the quantity of permanganate required is decreased [probably to the amount required by equation (2)], and is only increased again on acidification of the solution.

The atmospheric oxidation of alkaline solutions of sodium α-oxyhyponitrite is an extremely rapid process. In preparing the solutions for curves *A* and *B*, about 0·1 g. of the pure salt was placed in a 100-ml. graduated flask, which was then filled with 0·1N-sodium hydroxide (prepared from recently distilled water) and stoppered, leaving not more than 10 ml. of air space. As soon as the solid had dissolved the solution was shaken, and poured immediately (through air) into the silica cell of the spectrophotometer. Nevertheless, the ε values for curves *A* and *B* at 365 mμ indicate that the sodium α-oxyhyponitrite in these solutions was oxidised to nitrite to the extent of 7·5 and 14·0%, respectively. The decomposition represented by curves *D* (60% after 11 days) and *E* (99% after 12 weeks) is not therefore a measure of the true rate of oxidation, but is determined by the extent to which air is admitted to contact with the solution during the withdrawal of samples.

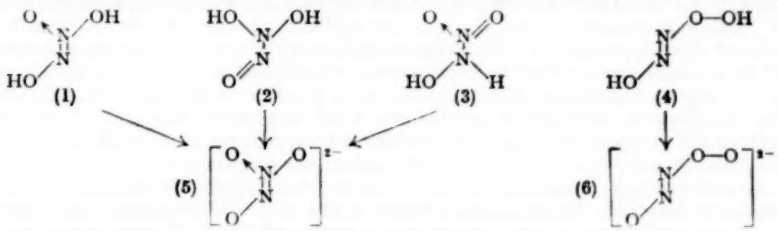
It is of interest that each of the curves *A*, *B*, *D*, *E*, and *F* passes through an isosbestic point at 314 mμ, where ε = 18·4. This is in accord with the presence, in each solution, of only two absorbing groups (α-oxyhyponitrite and nitrite). Curve *C* also passes through this point, so that the solutions used by Kortum and Finckh (*loc. cit.*) also contained these

two absorbing groups only. The ε value for curve *C* at 365 mμ indicates 41·3% decomposition to nitrite. A similar result is obtained by comparison of ε (curve *C*) at 260 mμ (ε = 3550) with the true value. Kortum and Finckh (*loc. cit.*) make no reference to precautions taken in the preparation of solutions, and in view of the rapidity of atmospheric oxidation, it is quite possible that their solutions could contain this relatively high concentration of nitrite.

In order to obtain a true absorption curve for sodium α-oxyhyponitrite experimentally, it would be necessary to carry out the measurements in the complete absence of atmospheric or dissolved oxygen. The experimental difficulties involved are considerable, and such measurements were not carried out since the true curve may be readily obtained by calculation. For example, curve *A* was at this stage known to be a composite curve, obtained from a solution of known composition; ε values obtained after subtraction of the absorption due to the 7·5% decomposition to nitrite were then multiplied by 100/92·5 to give the curve corresponding to pure sodium α-oxyhyponitrite. This is shown in Fig. 3 by the broken curve *G*, which has one peak at 250 mμ, and log $\varepsilon_{max.} = 3{\cdot}92$.

Structural Implications.—The value of $\lambda_{max.}$ for sodium hyponitrite (248 mμ) is close to the value given by some other compounds having N:N bonds; *e.g.*, 252 mμ for ethyl diazoacetate (Hantzsch and Lifschitz, *Ber.*, 1912, **45**, 3011; Wolf, *Z. physikal. Chem.*, 1932, *B*, **17**, 46), and 245 mμ for azomethane (Morton, "Practical Aspects of Absorption Spectrophotometry," Royal Inst. of Chem. Lecture, 1938, p. 35). Although other bonds in the molecule may modify the absorption, the curve suggests that the dominant absorption is due to the N:N bond. This is in accord with the generally accepted structure HO·N:N·OH for the acid (see, *e.g.*, Partington, "General and Inorganic Chemistry," Macmillan, 1947, p. 586).

The true absorption curve for sodium α-oxyhyponitrite shows only one peak, and $\lambda_{max.}$ is identical with that for sodium hyponitrite. This fact, together with the general similarity of the shape of the two curves, suggests that the N:N bond is also the dominant feature in the structure of the α-oxyhyponitrite ion, and that the structure is closely related to that of the hyponitrite ion. There is at present no generally accepted structure for α-oxyhyponitrous acid. Postulated structures are shown by (1)—(4). Structures



(1) and (2) are considered by Kortum and Finckh (*loc. cit.*). Partington (*op. cit.*, p. 587) considers (3) (the nitrohydroxylamine formula) and (4) as possible alternatives. Whatever the structure of the pure acid may be, structures (1), (2), and (3) each give rise to the bivalent ion (5), or to its resonance forms. Of the three possible resonance forms, only one gives an ion having the N:N bond, and the absorption curve suggests that the probable structure for the ion is as shown in (5). The ion (6), obtained from acid structure (4), also contains this bond; but the acidic character of a hydrogen atom attached to a peroxy-group [as in structure (4)] is generally much less that that of the hydrogen atom in :N·O·H, so that on structure (4) it is to be expected that the monobasic ion $(HN_2O_3)^-$ would be a common feature in the products of reaction of the acid with alkalis. However, there appears to be little evidence of this, and reaction of the acid or its sodium salt with bivalent cations gives precipitates of the type BaN_2O_3. On such evidence, the hydrogen atoms are regarded as combined in the acid molecule in a similar manner, which is the case in formulæ (1) and (2) only. Atmospheric oxidation to two nitrite ions in alkaline solution is also more readily reconciled with ion (5) than with (6). [The possibility that structure (6) represents the β-oxyhyponitrite ion is discussed in the following paper.]

Experimental

Absorption Curves.—The absorption spectra of solutions were measured by using a Unicam S.P. 500 spectrophotometer and 1-cm. silica cells. A hydrogen-discharge lamp, giving a continuous spectrum, was used as a light source. In each measurement the blank cell was filled with the same solution of " AnalaR " sodium hydroxide as was employed in the preparation of the test solutions.

Preparation of Sodium Hyponitrite.—Sodium hyponitrite was prepared by reduction of sodium nitrite in a modification of the method due to Divers (*J.*, 1899, **75**, 87) and Partington and Shah (*loc. cit.*). 25 G. of " AnalaR " sodium nitrite were dissolved in 40 ml. of water contained in a stout 1-l. flask. Sodium amalgam (prepared by dissolving 25 g. of clean sodium in 140 ml. of mercury) was added slowly with constant agitation of the flask and cooling in ice-water. The mixture was then transferred, in a stream of nitrogen gas to prevent absorption of carbon dioxide by the alkaline liquid, to a thick-walled separating funnel and shaken until gas evolution ceased. During the latter stage of the reduction process the aqueous phase changed from a voluminous foam to a suspension of fine crystals in a syrupy liquid which could readily be separated from the mercury layer. The liquor was run off into a beaker containing 800 ml. of ethyl alcohol, the tip of the funnel being held beneath the surface of the alcohol to avoid exposure to the atmosphere. Any liquor and crystals adhering to the walls of the funnel were quickly washed through with two 5-ml. portions of water. After being stirred vigorously for several minutes, the lower layer was transformed into a paste, which on trituration produced white sand-like crystals of hydrated sodium hyponitrite. The crystals were filtered off and dissolved in the minimum of water (about 8 ml.), and the solution was filtered to remove droplets of mercury, the product then being obtained from the filtrate by precipitation with alcohol as described above. The crystals were finally filtered into a sintered-glass crucible and washed with alcohol and ether, and the ether removed in a vacuum-desiccator. Anhydrous sodium hyponitrite (about 1 g.) was obtained by further drying for several days (over P_2O_5) and finally in an air-oven, the temperature of which was raised from 60° to 120° during several hours. The temperature of the oven was then kept at 120° (for about 2 hours) until the hyponitrite attained constant weight.

The above method comprises a refinement in the preparative techniques of earlier workers and combines the advantages of both rapidity and purity of product. Of the likely impurities due to this general method of preparation, sodium nitrite (from unchanged starting material) and sodium hydroxide are eliminated at the precipitation stage because of their solubility in alcohol. Sodium carbonate, arising from the absorption of atmospheric carbon dioxide by the alkaline liquor, is, however, not so readily eliminated and once formed it is precipitated together with the hyponitrite, and cannot be removed by recrystallisation. It is therefore essential to guard carefully against its formation at all stages of the preparation; the technique described above has been found to provide a product free from detectable carbonate. The treatment of the entire alkaline liquor with alcohol was found to be preferable to the method of Partington and Shah (*loc. cit.*) in which the crystals first formed are filtered off and dissolved in water, and the solution is concentrated in a vacuum-desiccator until the octahydrate is formed, before trituration with alcohol. By the present method, not only is the possible time of contact with the atmosphere reduced to the minimum, but the yield of sodium hyponitrite is increased and the preparation greatly expedited. It was found necessary to give the product a preliminary drying (P_2O_5) at room temperature for several days before finally drying it at 120°, for if attempts were made to dry the material too rapidly the hyponitrite partly melted in the remaining water of crystallisation and decomposed to sodium hydroxide. Although sodium carbonate impurity may arise from reaction of carbon dioxide with solid sodium hyponitrite as well as with alkaline solutions, the quantity of carbon dioxide in the atmosphere of the oven was insufficient to produce detectable carbonate over the period of several hours required. Provision of a soda-lime guard tube to the vessel containing the hyponitrite during the drying process is undesirable in that escape of water vapour is restricted and the salt again decomposes in the water of crystallisation.

Analysis of Sodium Hyponitrite.—(a) *Qualitative.* In view of the difficulties incurred in the quantitative analysis, it has been found that the most convenient assessment of batch purity of sodium hyponitrite is by means of qualitative tests for impurities likely to arise from materials used in the preparation. Nitrite may readily be detected in the presence of hyponitrite by liberation of iodine from potassium iodide solutions acidified with dilute sulphuric acid. In accordance with Oza's observations (*J. Indian Chem. Soc.*, 1945, **22**, 225), we have found that the hyponitrite ion does not liberate iodine immediately. Since hydrolysis of sodium

hyponitrite produces a highly alkaline solution, simple pH tests do not reveal the presence of sodium hydroxide impurity. The addition of silver nitrate solution, however, provides a means of detecting excess of alkalinity. Whereas pure sodium hyponitrite in aqueous solution reacts to provide the canary-yellow flocculent precipitate characteristic of silver hyponitrite, traces of sodium hydroxide impurity produce a marked difference in the colour and flocculation of the precipitate. Addition of small amounts of silver nitrate solution to a solution of sodium hyponitrite containing added alkali produced an instantaneous brown precipitate which rapidly changed on shaking to the yellow of silver hyponitrite, the colour reverting to brown only when excess of the reagent was added.

(b) *Quantitative.* The sodium content was determined as sulphate (Found: Na, 43·35. Calc. for $Na_2N_2O_2$: Na, 43·39%). Although the presence of either sodium nitrite (Na, 33·33%) or sodium hydroxide (Na, 57·49%) would be readily detected by their effect upon the sodium content, traces of sodium carbonate would not be detected in this way, since the sodium content and molecular weights of sodium hyponitrite and sodium carbonate are identical. Sodium content is not therefore sufficient in itself for the determination of purity, and a knowledge of the nitrogen or $N_2O_2^{2-}$ content is also desirable. Partington and Shah (*loc. cit.*) found the standard methods of nitrogen determination to be unsuitable and determined the hyponitrite content gravimetrically as $Ag_2N_2O_2$; this method has been employed in the present work. Somewhat low values are obtained owing to the slight solubility of silver hyponitrite in water (Mellor, "Treatise, etc.," Vol. VIII, p. 413). 0·1849 G. of the dried sodium salt was dissolved in 8 ml. of water, and silver nitrate solution added in slight excess. The flocculent yellow precipitate was filtered into a sintered-glass crucible (porosity 4), washed with two 5-ml. portions of cold water, and dried in a vacuum-desiccator to constant weight (0·4700 g.). This is equivalent to a $N_2O_2^{2-}$ content in the sodium salt of 55·4% (Calc. for $Na_2N_2O_2$: N_2O_2, 56·61%). Silver hyponitrite is not sufficiently stable to permit drying in an oven, and its solubility in organic liquids precludes alcohol–ether washing. The absence of silver nitrite in the precipitate was confirmed by conversion of 0·3443 g. of silver hyponitrite into 0·3570 g. of silver chloride (Found: Ag, 78·03. Calc. for $Ag_2N_2O_2$: Ag, 78·25%). The purity of sodium hyponitrite may also be determined satisfactorily by direct titration with standard hydrochloric acid (Oza, Dipali, and Oza, *loc. cit.*). By this method, with methyl-orange screened with xylene-cyanol F.F., and at room temperature, the prepared sodium hyponitrite was found to be 100% pure. This titration method does not reveal the presence of sodium carbonate as impurity, but it was not possible by any qualitative test to detect the presence of carbonate in the hyponitrite.

Preparation of Sodium α-Oxyhyponitrite.—Sodium α-oxyhyponitrite was prepared by Angeli's method (*loc. cit.*), involving the interaction of hydroxylamine, ethyl nitrate, and sodium ethoxide in ethanol solution. A concentrated solution of sodium ethoxide (9 g.) in ethanol was added to a saturated solution in ethanol of hydroxylamine hydrochloride (3 g.). The sodium chloride precipitated was filtered off, and 4 g. of ethyl nitrate were added to the filtrate at room temperature. A finely-divided suspension of sodium α-oxyhyponitrite was formed, the yield increasing as the liquid was cooled. After several hours, the crystals were filtered into a sintered-glass crucible (porosity 4) and washed with alcohol. They were then recrystallised twice by dissolving them in 2 ml. of water and adding a large excess of ethyl alcohol, as described above for the hyponitrite. The crystals (about 1 g.) were finally dried by washing them with ether, removing the ether in a vacuum-desiccator, and drying to constant wt. at 120°.

Sodium α-oxyhyponitrite so prepared was found to be free from impurities. Neither the mother-liquor nor the product absorbs or reacts with carbon dioxide, so that sodium carbonate does not interfere with this preparation. Any unchanged starting materials are eliminated on account of their solubility in ethanol. In view of the ready solubility of sodium α-oxyhyponitrite in water, it was necessary to dry the alcohol and ethyl nitrate thoroughly. However, contrary to Angeli's observations (*loc. cit.*), the salt is not of such a hygroscopic nature as to preclude purification by recrystallisation, provided that a small volume of water and a large excess of dry alcohol are employed.

Analysis of Sodium α-Oxyhyponitrite.—The sodium content of the dry salt was determined as sodium sulphate (Found: Na, 37·85. Calc. for $Na_2N_2O_3$: Na, 37·70%). The radical $N_2O_3^{2-}$ cannot be determined as the silver salt on account of the almost instantaneous reduction to silver, and the rapid fading of the characteristic red colour produced with uranyl nitrate does not permit colorimetric estimation. The nitrogen content, however, can readily be determined by Dumas's method (Found: N, 22·8, 23·0. Calc. for $Na_2N_2O_3$: N, 22·95%).

THE UNIVERSITY, NOTTINGHAM. [*Received, August 9th*, 1951.]

71. *The Oxidation of Sodium Hyponitrite and Sodium α-Oxyhyponitrite with Dinitrogen Tetroxide.*

By C. C. Addison, G. A. Gamlen, and R. Thompson.

The paper describes the preparation, and some properties, of a series of compounds $Na_2N_2O_x$, where x has values between 2 and 6.

Sodium hyponitrite ($Na_2N_2O_2$) is oxidised rapidly by liquid dinitrogen tetroxide to sodium β-oxyhyponitrite (β-$Na_2N_2O_3$), which differs in chemical properties from the α-compound prepared from hydroxylamine and ethyl nitrate.

Sodium α-oxyhyponitrite also undergoes rapid oxidation to the compound $Na_2N_2O_4$, which is readily distinguished from sodium nitrite. This compound undergoes slow secondary oxidation by liquid dinitrogen tetroxide to a compound having empirical formula $NaNO_3$. This may be the dimer $Na_2N_2O_6$, and a silver salt believed to have the formula $Ag_2N_2O_6$ has been prepared.

Sodium β-oxyhyponitrite undergoes slow oxidation with liquid dinitrogen tetroxide to the compound $Na_2N_2O_5$. The same product is formed rapidly by the action of nitrogen dioxide gas at 100° on sodium hyponitrite. The compound $Na_2N_2O_5$ is slowly oxidised by nitrogen dioxide gas at 100° to the $NaNO_3$ (or $Na_2N_2O_6$) stage.

The hydrolysis products of these compounds have been identified and estimated from measurements of the ultra-violet absorption spectra of their aqueous solutions. An attempt is made to correlate possible structures for the compounds with their mode of aqueous decomposition.

During many experiments involving liquid dinitrogen tetroxide (*J.*, 1949, S 211 *et seq.*), it was observed that both nitrate and nitrite ions are quite stable in liquid dinitrogen tetroxide. In view of the strongly oxidising character displayed by the tetroxide towards many organic compounds (Riebsomer, *Chem. Reviews*, 1945, **36**, 157) the stability of the nitrite ion is somewhat surprising. In order to determine whether stability towards dinitrogen tetroxide is a common property of the nitrogen oxyacid ions, the liquid tetroxide was added to dry samples of sodium α-oxyhyponitrite ($Na_2N_2O_3$) and sodium hyponitrite ($Na_2N_2O_2$), compounds in which the nitrogen atoms are in a lower state of oxidation. Preliminary experiments indicated that each compound was immediately oxidised to a product containing one additional atom of oxygen.

The product ($Na_2N_2O_4$) obtained by oxidation of sodium α-oxyhyponitrite had chemical properties quite different from those of sodium nitrite, and appeared therefore to be the sodium salt of a new nitrogen oxyacid of formula $H_2N_2O_4$. The product ($Na_2N_2O_3$) obtained by oxidation of sodium hyponitrite had chemical properties different from the sodium α-oxyhyponitrite prepared (as described in the preceding paper) from hydroxylamine and ethyl nitrate, from which it appeared that the ion $N_2O_3^{2-}$ might exist in two distinct forms. The products of each of these two rapid oxidations underwent slow secondary oxidation by dinitrogen tetroxide, to an extent which suggested the formation of other new compounds containing a higher proportion of oxygen.

With the exception of the sodium salt of nitroxylic acid, H_2NO_2, described by Maxted (*J.*, 1917, **111**, 1016), there has been no appreciable extension to the field of nitrogen oxyacids since before 1900. The possible existence of a new family of oxyacids of nitrogen gave added significance to the preliminary experiments outlined above. The oxidation of sodium hyponitrite and α-oxyhyponitrite has therefore been studied in greater detail. The existence of sodium salts of two new acids has been confirmed, and the existence of others is possible.

Oxidation of Sodium Hyponitrite.—In aqueous solution sodium hyponitrite is known to undergo oxidation to nitrate (*e.g.*, by potassium permanganate in acid solution) or to nitrite (by alkaline permanganate), but there is no evidence of any intermediate stages of oxidation

under these conditions; *e.g.*, there is no reference in the literature to the oxidation of hyponitrite to oxyhyponitrite in aqueous solution. However, in liquid dinitrogen tetroxide the oxidation can be arrested at an intermediate stage corresponding to the formation of a compound $Na_2N_2O_3$. The reaction was found to proceed as follows: 5 ml. of liquid tetroxide were added rapidly, in a closed system, to about 0·1 g. of carefully dried sodium hyponitrite in the form of a finely crystalline white powder (prepared as described in the preceding paper). The reaction was strongly exothermic, sufficient heat being generated to cause rapid boiling of the tetroxide. Nitric oxide was evolved. When reaction ceased after 2—3 minutes, the liquid was decanted, and the tetroxide gas removed in a stream of dry nitrogen; the product remained as a free-flowing, finely divided, white powder, its weight corresponding to the addition of one atom of oxygen. When this experiment was repeated with the reaction tube immersed in a freezing mixture, reaction was still rapid; under these conditions the nitric oxide produced by reduction of the tetroxide was partly retained in the liquid, which developed the clear green-blue colour characteristic of dinitrogen trioxide–tetroxide mixtures. If only a few drops (instead of several ml.) of tetroxide were added to the sodium hyponitrite, the heat of reaction could not then be dissipated by vapourisation of the tetroxide, and sufficient heat was produced partly to fuse the solid. This initial reaction clearly involves the transfer of oxygen from the tetroxide to the sodium hyponitrite. The number of nitrogen atoms does not change during reaction, as shown by the fact that the ultimate product of oxidation (*i.e.*, on allowing the $Na_2N_2O_3$ to react further) is sodium nitrate in a quantity equivalent to the sodium and the nitrogen content of the sodium hyponitrite originally taken for reaction. The same reaction takes place between sodium hyponitrite and gaseous dinitrogen tetroxide, but measurements recorded below show that reaction with the gas is more rapid than with the liquid. In the case of the gaseous reaction, more than one atom of oxygen per molecule of hyponitrite is rapidly added, and it is only with the liquid tetroxide that the reaction can be arrested after the addition of a single atom of oxygen. For this reason, the addition of liquid tetroxide to the hyponitrite was carried out rapidly under conditions in which the amount of preliminary reaction between solid and gaseous dinitrogen tetroxide was negligible.

The oxidation process will be considered under two headings: (*a*) primary oxidation, involving the initial rapid oxidation by the liquid tetroxide, and the formation of the compound $Na_2N_2O_3$, and (*b*) secondary oxidation, involving the slow oxidation of the compound $Na_2N_2O_3$.

Primary oxidation: sodium β-oxyhyponitrite.

The liquid tetroxide was removed immediately following the completion of the initial reaction, and the increase in weight of the solid determined. Typical results are:

Experiment	(1)	(2)	(3)	(4)	(5)	(6)	(7)
(A) $Na_2N_2O_2$ (g.)	0·1038	0·1126	0·0851	0·0692	0·1584	0·1567	0·1627
(B) Product (g.)	0·1192	0·1291	0·0988	0·0794	0·1854	0·1812	0·1878
Ratio (B)/(A)	1·149	1·147	1·161	1·148	1·170	1·156	1·154

The theoretical ratio $Na_2N_2O_3/Na_2N_2O_2$ is 1·151, and the mean of the above results (1·155) is in close agreement with this ratio.

The possible nature of products which could give rise to this 1·151 ratio may be summarised by the following equations; each is consistent with the addition of one atom of oxygen per molecule of hyponitrite:

$$Na_2N_2O_2 + O = Na_2N_2O_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$2Na_2N_2O_2 + 2O = Na_2N_2O_2 + 2NaNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$3Na_2N_2O_2 + 3O = 2Na_2N_2O_2 + NaNO_2 + NaNO_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$Na_2N_2O_2 + O = NaNO_2 + NaNO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

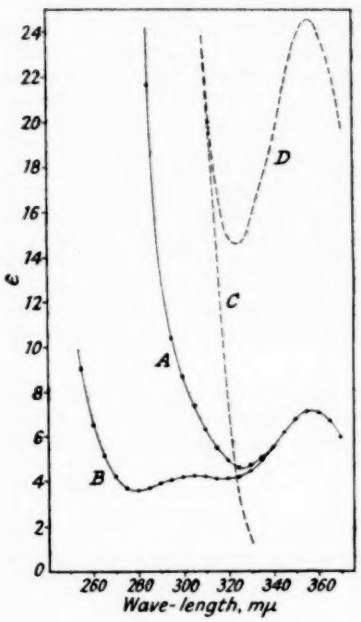
In order to distinguish between these various possibilities, the chemical reactions of the product (in particular its reactions with water) were studied. (As in the preceding paper, the compound $Na_2N_2O_3$ obtained by oxidation of sodium hyponitrite is termed sodium β-oxyhyponitrite, to distinguish it from the α-compound prepared from hydroxylamine and ethyl nitrate.)

Properties of Sodium β-Oxyhyponitrite.—The addition of water to this compound resulted

in an immediate and considerable effervescence. The solid particles were readily wetted, and the mode of evolution of gas was similar to that of carbon dioxide in a carbonate–dilute acid reaction (cf. the compound $Na_2N_2O_4$). The evolved gas was colourless and appreciably soluble in water, indicating nitrous oxide (this is confirmed quantitatively below). Neutral solutions of sodium α-oxyhyponitrite undergo slow decomposition but there is no effervescence when the solid is added to water, and the decomposition proceeds over a period of weeks. Moreover, alkaline solutions of the α-oxyhyponitrite decompose to nitrite only ($Na_2N_2O_2 + O = 2NaNO_2$).

The vigorous effervescence with water enables equations (2) and (3) to be dismissed, since the aqueous decomposition of sodium hyponitrite is also slow. Again, sodium β-oxyhyponitrite is quite insoluble in absolute alcohol, whereas sodium nitrite is appreciably soluble. The insolubility in alcohol also dismisses equation (4), although the reaction with water is in some respects similar to that of sodium nitrosyl: $NaNO + H_2O = NaOH + N_2O$ (Joannis, *Ann. Chim. Phys.*, 1894, **118**, 713; Zintl and Harder, *Ber.*, 1933, **67**, 760). If equation (4) were correct, the hydrolysed compound should contain 56% of sodium nitrite, and this quantity should not decrease as a result of secondary oxidation; results discussed below show that this is not the case.

FIG. 1.



Sodium β-oxyhyponitrite is therefore to be regarded as a single compound. It can be further distinguished from the α-compound by the action of silver nitrate and of uranyl nitrate on the aqueous solutions. When silver nitrate solution is added to an aqueous solution of the α-compound, at room temperature, the transient yellow precipitate first formed changes almost immediately to a black precipitate of silver. (This change is accompanied by effervescence, and probably results from the auto-reduction of silver oxide by the α-oxyhyponitrite ion, with evolution of oxygen.) With the β-compound, a stable yellow precipitate of silver hyponitrite is obtained provided that the silver nitrate is not in excess. Addition of excess of silver nitrate results in a brown precipitate of silver oxide, produced by the sodium hydroxide which is one product of hydrolysis of sodium β-oxyhyponitrite. Uranyl nitrate solution produces, with solutions of the α-compound, a deep red colour which fades in dilute solution to pale yellow after several minutes. With the β-compound no colour is produced, but on storage a yellow precipitate of sodium diuranate is formed, owing again to the alkalinity of the β-oxyhyponitrite solutions.

Products of Aqueous Decomposition.—Curve *A* (Fig. 1) shows the ultra-violet absorption spectrum of the freshly prepared solution of sodium β-oxyhyponitrite in 0·1N-sodium hydroxide solution, and curve *B* is the spectrum obtained when the solution had been kept for 18 days. The solution was prepared under exactly the same experimental conditions as were employed for the preparation of solutions of the α-compound, the corresponding curves for which are superimposed for comparison in Fig. 1: curve *C* was obtained with the freshly prepared solution and curve *D* with an 11-day old solution.

The curves (*A* and *C*) for the fresh solutions are clearly quite different and the aqueous solution of the β-oxyhyponitrite originally contains a greater quantity of nitrite than is present in the solution of the α-compound. Decomposition of the α-oxyhyponitrite solution on standing leads to a considerable increase in nitrite content, whereas the nitrite content of the solution of the β-compound remains unchanged. Curve *A* is consistent with the presence of sodium hyponitrite, nitrite, and nitrate in the solution, the change to curve *B* on standing arising from the decomposition of the hyponitrite to nitrous oxide and sodium hydroxide. Formation of the latter by this means does not influence the absorption curves, since the hydroxide ion does not absorb over this wave-length range (and the solutions are prepared in sodium hydroxide solution). Curve *B* reveals the presence of nitrate in the solution by the appearance of a peak at 302·5 mμ; no nitrate is obtained as a result of aqueous decomposition of the α-compound.

Analysis of the solution of sodium β-oxyhyponitrite by the methods outlined in the preceding paper gave the following results :

	$Na_2N_2O_2$	$NaNO_2$	$NaNO_3$
G.-mols. produced from 1 g.-mol. of β-$Na_2N_2O_3$	0·13	0·55	0·26
N content (g.-atoms) of solution	0·26	0·55	0·26

From these results it is clear that the nitrogen content of the solution (1·07 g.-atoms) is only about half of the nitrogen originally added as β-oxyhyponitrite; the remainder may be regarded as lost from the system in the form of nitrous oxide. In the decomposition of sodium salts of nitrogen oxyacids, the evolution of nitrous oxide must involve the formation of an equivalent quantity of sodium hydroxide in solution. This has been confirmed by direct titration of the solution. Oza, Dipali, and Oza (*J. Indian Chem. Soc.*, 1950, **27**, 409) have shown that sodium hyponitrite may be determined by titration with solutions of strong mineral acids; the quantity of acid required to titrate a solution of sodium β-oxyhyponitrite will therefore be the sum of that required for the hyponitrite and the sodium hydroxide produced on reaction with water. When 0·1 g. of sodium β-oxyhyponitrite was dissolved in water, 9·8 ml. of 0·1N-hydrochloric acid solution were required for titration. (The end-point is somewhat confused by the presence of nitrite in the solution, but is sufficiently accurate for present purposes.) By reference to the sodium hyponitrite content as determined from the absorption curves, it may be calculated that 2·1 ml. of this titre was due to the sodium hyponitrite. It is thus seen that the remaining 7·7 ml. of hydrochloric acid are equivalent to the production, in solution, of 0·94 g.-mol. of sodium hydroxide per g.-mol. of sodium β-oxyhyponitrite. From the results in the above table, it may also be calculated from the loss in nitrogen content that 0·47 g.-mol. of nitrous oxide is produced by reaction of 1 g.-mol. of sodium β-oxyhyponitrite with water.

The quantities recorded above are suitably related if we assume that hydrolysis proceeds primarily in accordance with the equation

$$\overset{(2)}{2Na_2N_2O_3} + H_2O = \overset{(1\cdot10)}{2NaNO_2} + \overset{(1\cdot88)}{2NaOH} + \overset{(0\cdot94)}{N_2O} \quad . \quad . \quad . \quad . \quad (5)$$

but that in addition during the rearrangement of the fragments of the β-oxyhyponitrite ion, some $NaNO_2$ fragments disproportionate to give nitrate and hyponitrite :

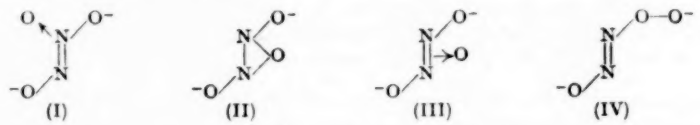
$$4NaNO_2 = \overset{(0\cdot26)}{Na_2N_2O_2} + \overset{(0\cdot52)}{2NaNO_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The numbers given in parentheses above the equations represent the number of g.-mols. of each compound produced from 2 g.-mols. of sodium β-oxyhyponitrite; the sodium hydroxide and nitrous oxide values are close to those required by equation (5), and the relative quantities of nitrate and hyponitrite bear the appropriate 2 : 1 ratio required by such a disproportionation. From equation (6), 1·04 g.-mols. of $NaNO_2$ fragments disproportionate, and the total nitrite obtained (2·14 g.-mols.) by adding this value to the nitrite observed to be present in the solution is close to the requirements of equation (5).

It is of interest that reaction (5) has been postulated by Naik, Shah, and Patel (*J. Indian Chem. Soc.*, 1946, **23**, 284) as a method of decomposition of neutral solutions of sodium α-oxyhyponitrite. Even so, the decomposition is slow, and in sharp contrast to the vigorous reaction of the β-compound in contact with water. Again, in the decomposition of the β-compound, sodium nitrate and hyponitrite are produced in a quantity equivalent to half the sodium nitrite required by equation (5); Angeli and Angelico (*Atti R. Accad. Lincei*, 1901, **10**, 249) postulate six ways in which the α-oxyhyponitrite could decompose under varying conditions, but none of the reactions involves the formation of nitrate as a reaction product.

Structure, and Mechanism of Aqueous Decomposition.—The major obstacle in the study of the mechanism of decomposition in water is the lack of conclusive evidence for the structure of the two forms of sodium oxyhyponitrite. In the preceding paper, structure (I) was considered to be the most suitable for the α-oxyhyponitrite ion. Structure (II) involves a three-membered ring which is unlikely to be stable, and by fission of either of the N–O ring bonds the structure reverts to (I). Structure (III), involving π-bonding

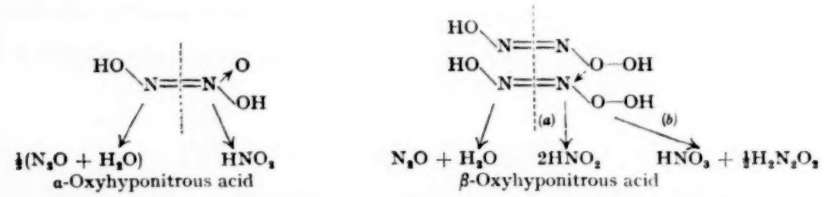
of the additional oxygen atom, differs from (I) in electronic rather than atomic distribution, and both structures (II) and (III) are therefore so similar to (I) that their chemical properties would be unlikely to differ considerably from those of the α-oxyhyponitrite ion. It is possible, however, that an ion having structure (IV) might differ significantly in chemical behaviour from (I), and the aqueous decomposition of the sodium salts will be considered in the light of this structure.



(I) (II) (III) (IV)

In the acid corresponding to structure (IV), the :NO·OH group will be more weakly acidic than the :N·OH group. The acid corresponding to structure (I) contains only :N·OH groups, and in consequence the sodium salt of ion (IV) would be more readily hydrolysed than the salt of ion (I), to give rise to a less stable acid. This is in agreement with experimental observations.

The production of nitrite in solution indicates that fission of both the α- and the β-acid must occur at the ·N:N· bond, and such hydrolytic fission may be represented diagrammatically as :



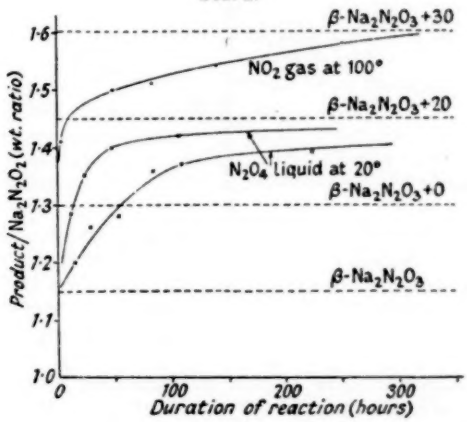
Of the two fragments resulting from fission of the α-acid, one fragment requires only an electronic rearrangement to give nitrous acid. This agrees with the observation that neither nitric nor hyponitrous acid is produced by this decomposition. The unstable NOH fragment, when produced under these conditions, may be regarded as giving rise directly to nitrous oxide. (The NOH group is probably also an intermediate in the aqueous decomposition of sodium nitrosyl.) The total decomposition is then represented by equation (5). The same fragment, in the same proportion, results from ·N:N· fission of β-oxyhyponitrous acid. However, the second (NO·OH) fragment is required to undergo atomic rearrangement to give nitrous acid. During this rearrangement, it is possible that an atom of oxygen may be transferred from one fragment to another; if it is assumed that the intramolecular rearrangement (*a*) and the intermolecular rearrangement (*b*) proceed to equal extents, then nitrous, nitric, and hyponitrous acids are produced in the relative quantities required by equations (5) and (6).

It is to be inferred here that the suggested atomic rearrangements, or oxygen-atom transfers, take place more readily than those involving the release of oxygen as hydrogen peroxide, since the presence of hydrogen peroxide has not been detected in the solutions by qualitative tests, nor in spite of its appreciable absorption has it been detected during ultra-violet spectrophotometric analyses. It is difficult to formulate the compounds discussed here without resort to ·O·O· linkages, yet it is a characteristic property of most per-acids and their salts that they release hydrogen peroxide in solution. However, in the case of perdisulphuric or perdiphosphoric acid, normal oxyacid ions are linked by peroxy-bridges; there is no direct bonding between atoms of the typical elements, and no atomic rearrangement occurs on release of hydrogen peroxide. With these higher oxyacids of nitrogen the fission of the ·N:N· bond is considered to dominate their behaviour on hydrolysis, and the peroxy-properties are manifest in the transfer of oxygen atoms to other fission fragments rather than in the release of hydrogen peroxide.

SECONDARY OXIDATION: THE COMPOUNDS $Na_2N_2O_5$ AND $Na_2N_2O_6$.

Although sodium hyponitrite gains one atom of oxygen from dinitrogen tetroxide almost instantaneously, oxidation beyond this stage is slow. Fig. 2 shows the rate at which the sodium salt increases in weight. The two curves for secondary oxidation with liquid dinitrogen tetroxide were obtained with two samples of sodium hyponitrite separately prepared, but each sample was pure and dry. The curves illustrate the wide variation observed in the rates of secondary oxidation. This is attributed to such factors as the variation in particle size (*i.e.*, surface area) between different samples, and not to any difference in the nature of the reaction taking place, since the increase in weight has been found to be the only factor determining the chemical behaviour of the product. All such curves display the same features; beginning at the 1·15 ratio, the curves approach a ratio of 1·45, but no reaction involving the liquid tetroxide has been found to give rise to a weight ratio exceeding 1·45. The liquid reaction therefore produces ultimately a compound of empirical formula $Na_2N_2O_5$. The curves pass, without deflection, through the 1·3 ratio, and these experiments therefore suggest that the compound $Na_2N_2O_4$ is not significant in this reaction. The gaseous reaction (Fig. 2) provides additional support for the existence of the compound $Na_2N_2O_5$; when sodium hyponitrite is treated with the gaseous NO_2–N_2O_4 mixture, the solid rapidly gains three atoms of oxygen.

FIG. 2.



The curve shows a sharp break at a ratio of 1·45 (equivalent to $Na_2N_2O_5$) and the final atom of oxygen is taken up very slowly.

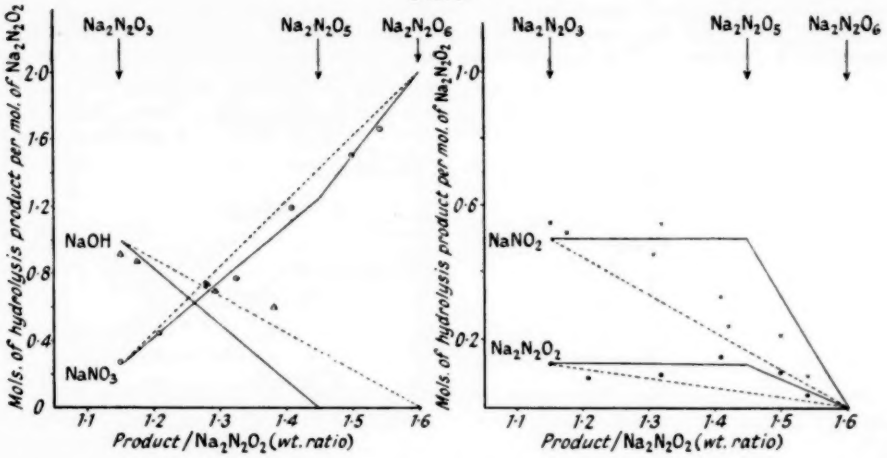
In order to obtain further evidence on the nature of the products formed during secondary oxidation, reactions of the products with water have been studied. A parallel series of oxidations was carried out, varying times being allowed for reaction. In each case the solid was freed from dinitrogen tetroxide, and the increase in weight determined. A portion of the solid was dissolved in water, and titrated with 0·1N-hydrochloric acid in order to determine total alkalinity. The remainder of the product was then dissolved in 0·1N-sodium hydroxide, and the ultra-violet absorption spectra of the solution were measured immediately, and again after several weeks. From these curves the nitrate, nitrite, and hyponitrite contents of the solution were calculated. The numbers of g.-mols. of each constituent thereby obtained from each g.-mol. of sodium hyponitrite originally taken are plotted in Fig. 3 against the increase in weight.

The results indicate that the same mechanism of oxidation probably applies to both the liquid and the gaseous reaction. The quantities of hydrolysis products recorded for Product/$Na_2N_2O_2$ ratios less than 1·45 were determined on solutions of oxidation products prepared by using liquid dinitrogen tetroxide. At ratios greater than 1·45, the product was prepared by using the gaseous reaction at 100°, and the experimental points for ratios above 1·45 are seen to represent a continuation of the trends shown by the values for lower ratios. This supports the belief that the mechanism of oxidation involves the NO_2, rather than the N_2O_4 molecule. The more rapid oxidation by gaseous than by liquid

dinitrogen tetroxide is also explained thereby, since the degrees of dissociation to nitrogen dioxide are 90 and <1·0%, respectively.

The Compound $Na_2N_2O_5$.—Three possible processes may take place during secondary oxidation : (1) The material produced by liquid tetroxide oxidation, empirical formula $Na_2N_2O_5$, could be an equimolecular mixture of sodium nitrate and sodium nitrite. (2) The liquid reaction may produce a single compound $Na_2N_2O_5$ which could then undergo further oxidation to $Na_2N_2O_6$ (or $NaNO_3$). (3) Secondary oxidation may involve only the direct oxidation of sodium β-oxyhyponitrite to nitrate. The first possibility may be dismissed, since analysis of the aqueous solution of the 1·45 ratio material (Fig. 3) shows nitrate and nitrite to be present in the molar ratio 1·3 : 0·25, rather than 1 : 1. Again, the product is insoluble in absolute alcohol, and separate experiments have shown that sodium nitrite is not oxidised by nitrogen dioxide at 100°.

FIG. 3.



The results in Fig. 3 afford some help in distinguishing between possibilities (2) and (3). Alternative structures for the acid $H_2N_2O_5$ are (V) and (VI). Structure (5) should

give rise to nitrate and nitrite in solution in equimolecular quantities; this is not the case. With structure (VI) (if we assume that disproportionation of the :NO·OH group proceeds to give 50% of HNO_2, as with β-oxyhyponitrous acid), the decomposition of the compound $Na_2N_2O_5$ in water should take place according to the equation

$$8Na_2N_2O_5 = 10NaNO_3 + 4NaNO_2 + Na_2N_2O_2 \quad . \quad . \quad . \quad . \quad . \quad (7)$$

This is to be compared with the equation

$$8\ \beta\text{-}Na_2N_2O_3 + 4H_2O = 2NaNO_3 + 4NaNO_2 + Na_2N_2O_2 + 8NaOH + 4N_2O \quad . \quad (8)$$

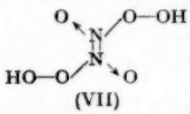
which represents the summation of equations (5) and (6).

The full lines in Fig. 3 represent the change in hydroxide and nitrate content [Fig. 3(*a*)] and in nitrite and hyponitrite content [Fig. 3(*b*)] of the aqueous solution obtained from a product considered to consist of a mixture of the compounds β-$Na_2N_2O_3$ and $Na_2N_2O_5$ in the ratio range 1·15—1·45, and a mixture of the compounds $Na_2N_2O_5$ and $NaNO_3$ in the ratio range 1·45—1·60. The broken lines represent the corresponding changes to be expected if sodium β-oxyhyponitrite undergoes secondary oxidation directly to sodium nitrate. The experimental values in Fig. 3 are somewhat scattered; this is probably an inevitable feature in experiments of this type,

since it is not possible to reproduce exactly the conditions of the vigorous reaction between the solid product and water, and the speed of solution will depend to some extent on the particle size of the powder. Nevertheless, attention should be directed to the following points concerning the position of the experimental values with respect to the full and the broken lines. (*a*) All nitrate values [Fig. 3(*a*)] lie below the broken line, and are close to the full line. This agrees with the formation of a $O\leftarrow\overset{\overset{O}{\|}}{N}—O—OH$ fragment on hydrolysis. (*b*) The hydroxide content falls with increasing ratio. As the titration decreases, the end-point error due to the presence of nitrite becomes considerable, so the hydroxide values recorded should not be regarded as serving to differentiate between the full and the broken lines; for this reason, hydroxide contents are not recorded beyond the 1·4 ratio. Although the quantity of nitrous oxide evolved on dissolution of the product was not measured directly, it was observed that effervescence markedly decreased as the weight ratio of the product increased. (*c*) With one exception, the hyponitrite values [Fig. 3(*b*)] fall above the broken line, and favour the full line. (*d*) All nitrite values lie above the broken line, but do not reach the full line. The latter was calculated on the assumption that during decomposition, half of the ·NO·OH fragments give rise to HNO_2 molecules. This quantitative analogy with the decomposition of sodium β-oxyhyponitrite may not be justified. During the decomposition of the acid $H_2N_2O_5$ a smaller proportion of the ·NO·OH fragments may yield HNO_2 molecules; this could bring the full line closer to the experimental values.

The evidence obtained from the study of aqueous solutions of the products of secondary oxidation, together with the more direct evidence in Fig. 2, may therefore be regarded as supporting (though inconclusively) the existence of a distinct compound of formula $Na_2N_2O_5$ which is the salt of an acid having structure (VI).

The Compound of Type $M_2N_2O_6$.—In view of the probable existence of the compound $Na_2N_2O_5$ (as well as the compound $Na_2N_2O_4$ discussed below) it is reasonable to consider the possibility that the ultimate oxidation of sodium hyponitrite with nitrogen dioxide is the compound $Na_2N_2O_6$, rather than sodium nitrate. This compound, whose acid we would formulate as (VII) by analogy with compounds in a lower state of oxidation, would be expected to give two molecules of $NaNO_3$ as a result of ·N:N· fission in water, since no other groups are present to which atoms of oxygen may be transferred. Acids $H_2N_2O_5$ and $H_2N_2O_6$ are suggested by Oddo (*Gazzetta*, 1915, **45**, 414) as being present in mixtures of liquid dinitrogen tetroxide and water, but are considered only as loose addition compounds of the component nitrous and nitric acids. Reference is made by Yost and Russell ("Systematic Inorganic Chemistry," Oxford Univ. Press, 1946, p. 65) to the ion $N_2O_6^{2-}$.



(VII)

Although no evidence for the existence of the dimeric form $M_2N_2O_6$ is available from a study of the sodium salt, it is possible to prepare a silver salt believed to have this formula.

Silver hyponitrite was prepared, as a yellow precipitate, by the action of silver nitrate on a 5% solution of sodium hyponitrite. The precipitate was dried to constant wt. over phosphoric oxide in a vacuum-desiccator, which was kept in the dark, since silver hyponitrite is photosensitive. Owing to its instability to heat, the compound could not be dried in an oven, and at least ten days' drying at room temperature was required; on addition of liquid dinitrogen tetroxide to dry silver hyponitrite, nitric oxide was evolved, the colour of the liquid changing to blue-green; the yellow colour of the solid became paler, without any other noticeable change in physical condition. The reaction was complete within a few minutes, and the increase in weight of the solid was then determined:

Expt.	$Ag_2N_2O_2$ (g.)	Product (g.)	Product/$Ag_2N_2O_2$ (by wt.)*
1	0·1211	0·1453	1·200
2	0·2209	0·2696	1·221

* Theoretical ratios: $Ag_2N_2O_3/Ag_2N_2O_2 = 1·058$; $Ag_2N_2O_6/Ag_2N_2O_2 = 1·228$.

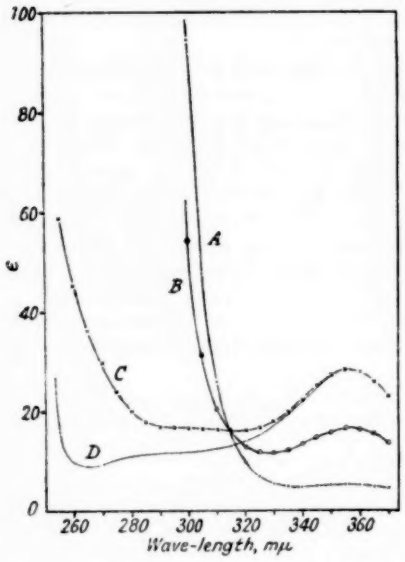
The silver content of the reaction product in Expt. (1) was found to be 64·6% ($Ag_2N_2O_6$ requires Ag, 63·5%). This is consistent with the fact that oxidation is not quite complete (Calc. for $Ag_2N_2O_2$: Ag, 78·4%). Oxidation of the silver salt therefore proceeds almost immediately to the $Ag_2N_2O_6$ stage, whereas corresponding oxidation of the sodium salt required 300 hours at 100°. The yellow colour, and solubility in organic solvents, of silver hyponitrite suggest

that the parent compound may be predominantly covalent in character. If this is so, oxidation of the covalent molecule rather than of the hyponitrite ion may well follow a different course, and may account for the striking difference in the rates of oxidation of the silver and the sodium salt. The reaction product was insoluble in cold water, and appeared to undergo no decomposition. In boiling water decomposition occurred to give soluble silver salts, leaving a black residue. This residue readily dissolved with effervescence in dilute nitric acid solution and was presumably silver and silver oxide. From this behaviour it is clear that the reaction product is not silver nitrate, but its properties are those expected of a compound $Ag_2N_2O_6$ having some covalent character. Unlike the behaviour of the corresponding sodium salt, treatment with water does not immediately give rise to the liberation and decomposition of the acid $H_2N_2O_6$. However, when the compound $Ag_2N_2O_6$ is dissolved directly in dilute sulphuric acid, the free acid is presumably produced; hydrolytic fission can then take place as with the sodium salts and analysis of the resulting solution showed the presence of no oxyacid ion of nitrogen other than nitrate.

Primary oxidation of sodium α-oxyhyponitrite.

Some examples of the difference in chemical properties between sodium α- and β-oxyhyponitrites have already been given. In addition, their behaviour towards liquid dinitrogen tetroxide is quite different. Although the β-compound undergoes the slow secondary oxidation considered above, yet the α-compound reacts immediately. When several ml. of the tetroxide were added to about 0·1 g. of sodium α-oxyhyponitrite, the colour of the liquid changed to blue-green; the reaction, which was strongly exothermic, was complete within a few minutes. On removal of the dinitrogen trioxide–tetroxide mixture, the solid was found to have increased in weight in a ratio of 1·13 ($Na_2N_2O_4/Na_2N_2O_3 = 1·131$). This ratio was readily reproducible, and the reaction may be represented by the equation : $\alpha\text{-}Na_2N_2O_3 + N_2O_4 = Na_2N_2O_4 + N_2O_3$.

Fig. 4.



It is of interest that, although the oxidation of sodium β-oxyhyponitrite passes through the $Na_2N_2O_4$ stage without hesitation, yet the reaction is readily arrested at this stage by oxidation of the α-compound.

Its chemical properties confirm that the compound is not sodium nitrite. The solid is not readily wetted by water. When water is added to a sample of the compound in a test-tube, the powder remains at the bottom; as the particles are wetted there is an evolution of gas. The small bubbles coalesce to one large one, which remains attached to the dissolving solid until it becomes large enough to break away. The effect is in marked contrast to the effervescence which occurs with sodium β-oxyhyponitrite. The gas was found to be nitrous oxide, and about 1 ml. of gas was liberated from 0·1 g. of solid during solution. The aqueous solution gave an instantaneous black precipitate with silver nitrate solution; treatment with uranyl nitrate solution produced the same deep red colour as was obtained with sodium α-hyponitrite.

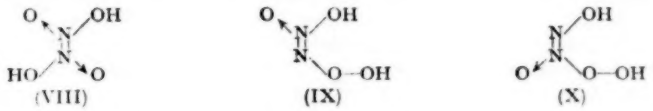
Products of Hydrolysis of the Compound $Na_2N_2O_4$.—The salt was dissolved in 0·1N-sodium hydroxide. Curve *A* (Fig. 4) shows the ultra-violet absorption spectrum obtained immediately after preparation of the solution, and curves *B* and *C* were obtained after the solution had been kept for 11 days and 3 months, respectively. The curves indicate the presence, in the original solution, of sodium α-oxyhyponitrite, sodium nitrate, and sodium nitrite. Applied quantitatively, it may be calculated from curve *A* that in the original solution 10·6% of the compound $Na_2N_2O_4$ has been converted into sodium nitrite. It has been shown in the preceding paper that the formation of quantities of sodium nitrite of this order is almost unavoidable in the preparation of solutions of sodium α-oxyhyponitrite. Since the fresh solution of the

compound $Na_2N_2O_4$ contains much α-oxyhyponitrite, the major portion of the sodium nitrite present in the original solution is regarded as arising from this cause. When the solution is kept, the α-oxyhyponitrite decomposes to nitrite only; the difference between the curve obtained on complete decomposition (curve *C*) and the pure sodium nitrite curve *D* is due to the nitrate contained in the solution.

The decomposition of the compound $Na_2N_2O_4$ in aqueous solution has been found to proceed as follows:

$$3Na_2N_2O_4 = \overset{(1\cdot95)}{2NaNO_3} + \overset{(1\cdot8)}{2Na_2N_2O_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

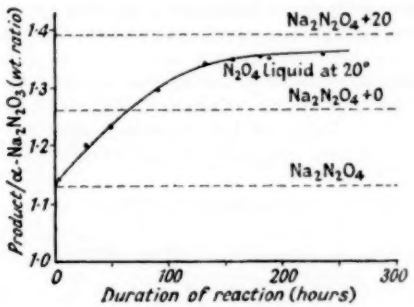
The figures in parentheses over equation (9) are the molar quantities of the compounds observed to be present in the original solution. The alternative structures for the acid



$H_2N_2O_4$ are (VIII), (IX), and (X). The fragments formed by fission of acids (VIII) and (IX) would give two and at least one molecules of nitrous acid, respectively, whereas nitrite is not a major constituent of the solutions; structures (X) is therefore considered to be more appropriate.

The fission of the N:N bond in one out of three $H_2N_2O_4$ molecules, with transfer of oxygen atoms, is in accord with equation (9). It is to be expected, as observed, that the product of this decomposition would produce α-, rather than β-, oxyhyponitrous acid. However, if we assume that the small quantity (0·2 mol.) by which the fresh solution is found to be deficient in α-oxyhyponitrite content represents the formation of β-oxyhyponitrite, it is possible to account for the evolution of nitrous oxide on aqueous decomposition of the compound $Na_2N_2O_4$. Since sodium β-oxyhyponitrite decomposes immediately in water according to equation (5), its presence would not be detected in the fresh solution, and calculation shows that the quantity of nitrous oxide evolved is approximately equivalent to 0·2 mol. of sodium β-oxyhyponitrite (equation 9).

FIG. 5.

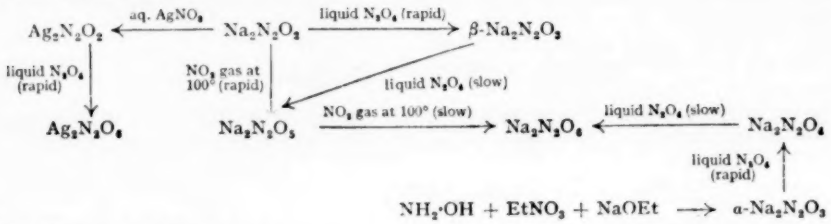


SECONDARY OXIDATION OF SODIUM α-OXYHYPONITRITE.

Oxidation by liquid dinitrogen tetroxide beyond the $Na_2N_2O_4$ stage is very slow; the fact that it does occur is further clear evidence that the compound $Na_2N_2O_4$ differs from sodium nitrite. Fig. 5 shows a typical curve relating weight ratio to time. The curve shows no break at the $Na_2N_2O_5$ stage (cf. the secondary oxidation of sodium β-oxyhyponitrite) but smoothly approaches the state of complete oxidation represented by $NaNO_3$ (or $Na_2N_2O_6$). Analyses of the reaction product at various stages in the ratio range 1·13—1·393 have been carried out by study of the ultra-violet absorption spectra of the aqueous solutions. They indicate that

the nitrate content of the solutions increases, and the α-oxyhyponitrite content diminishes, almost linearly with increasing ratio, so that oxidation of the compound $Na_2N_2O_4$ involves the slow addition of two further atoms of oxygen.

Conclusions.—The reactions and products described in this paper are summarised in the following scheme.



THE UNIVERSITY, NOTTINGHAM. [*Received, August 9th,* 1951.]

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72. *Studies with Dithizone. Part III.* The Extraction Constant of Zinc Dithizonate.*

By H. IRVING, C. F. BELL, and R. J. P. WILLIAMS.

The extraction of zinc as its dithizone complex into chloroform and carbon tetrachloride has been investigated for a wide range of reagent concentrations and from aqueous buffers of different pH and ionic strength. The extraction constants under the conditions of zero ionic strength are ~10 and 130 ± 4, respectively. Partition equilibrium has been approached for the first time from both sides, and the general and specific effects of salt present in the aqueous phase have been studied. The new data have been used to test theoretical equations previously deduced for the partition equilibria of metal complexes, and certain modifications are proposed when the activity coefficients of the reacting species must be taken into account or when water-soluble metal complexes participate in the partition equilibria. The composition of zinc dithizonate has been confirmed by spectrophotometric measurements, the method of continuous variations being used.

IF a solution of a monobasic organic acid, HR, in a solvent immiscible with water is shaken with an aqueous solution of an *n*-valent kation, M^{n+}, under such conditions that there results a metal complex, MR_n, soluble in organic solvents though sparingly soluble in water, the situation when partition equilibrium has been attained can be represented by:

$$[MR_n]_o/[M^{n+}]_w = E = K([HR]_o/\{H\}_w)^n \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

whence

$$\log_{10} E = \log_{10} K + n \log_{10} [HR]_o + n\text{pH} \quad . \quad . \quad . \quad . \quad (1b)$$

where the subscripts *w* and *o* refer to the aqueous and the organic phases, respectively. The assumptions made in deriving this equation have been discussed in a previous paper (Irving and Williams, *J.*, 1949, 1841) where it was shown that the extraction constant $K = (K_r p_r)^n/(K_e p_e)$, where K_r and K_e are the dissociation constants and p_r and p_e the partition coefficients between water and organic solvent of the reagent, HR, and complex, MR_n, respectively.

Experimental verification of equation (1) requires, in addition to measurements of the extractability, *E*, at various acidities, a knowledge of the term $[HR]_o$, the concentration of reagent in the organic phase *in excess* of that required for complex formation. Now if

* Part II, *J.*, 1949, 1847.

V_w, V_o are the volumes of aqueous and organic phases and M_{HR} is the total amount of reagent in the whole system (expressed in g.-mol.) we have

$$M_{HR} = V_w([HR]_w + [R']_w + n[MR_n]_w) + V_o([HR]_o + n[MR_n]_o)$$
$$= \left(V_w p_r(1 + K_r/\{H\}) + V_o\right)[HR]_o + n(V_w p_e + V_o)[MR_n]_o \quad . \quad . \quad (2)$$

A knowledge of p_r, K_r, and pH being assumed, the term $[HR]_o$ can obviously be calculated from the known total amount of reagent taken provided the second term in equation (2) can be neglected in comparison with the first, a condition which can be realised experimentally by using an amount of reagent which is very large in comparison with that of the metal extracted. Indeed, under conditions where $[HR]_o$ may be regarded as effectively constant, it follows from equation (1*b*) that a plot of $\log_{10} E$ against pH should be a straight line of which the integral slope, n, would confirm the empirical formula of the extractable species. This prediction has been confirmed by Suttle (Atomic Energy Commission Declassified Report 2800) for partition equilibria involving ^{140}La and 1-thenoyltrifluoroacetone (T.T.A.; cf. Irving, *Quart. Reviews*, 1951, V, 223).

If, however, the amount of metal extracted becomes comparable with the available amount of reagent, the problem becomes more complex. This is the case when diphenylthiocarbazone (" dithizone "; HDz) is used in trace-metal determinations, for since both the reagent and its metal complexes are strongly coloured, the sensitivity of absorptiometric determinations by reversion (Irving, Risdon, and Andrew, *J.*, 1949, 537) or by other methods (Sandell, " Colorimetric Determination of Traces of Metals," 2nd edn., New York, 1950) increases as the ratio $nV_o[MR_n]_o/M_{HR}$ approaches unity. Whilst on the one hand the high molecular extinction coefficient of dithizone (in carbon tetrachloride, $\varepsilon = 3{\cdot}5 \times 10^4$ at $\lambda_{max.} = 615$ mμ) facilitates the determination of $[HDz]_o$ by absorptiometry even in the presence of most of its strongly coloured metal complexes (which absorb comparatively feebly at this wave-length), yet instrumental considerations limit the useful concentration of dithizone to $<10^{-4}$M, a concentration which becomes comparable with the level of trace-metal concentrations involved, *viz.*, 0—10 p.p.m. On the other hand, dithizone fulfils two of the essential conditions postulated in deriving equation (1), for it has recently been shown (*a*) to exist as unassociated molecules in both aqueous and organic phases (Irving, Cooke, Woodger, and Williams, *J.*, 1949, 1847) and (*b*) to behave as a monobasic acid of pK about 4·5 (Irving *et al.*, *loc. cit.*; and unpublished work; Sandell, *J. Amer. Chem. Soc.*, 1950, **72**, 4660). Moreover, if the pH of the aqueous phase is at least 2 units below $pH_{\frac{1}{2}}$, the hydrogen-ion exponent for 50% extraction (8·9 and 10·6 for carbon tetrachloride and chloroform systems, respectively), less than 1% of the un-complexed dithizone will partitioni nto the aqueous phase so that the absorbancy * of the organic extract measured at $\lambda_{max.}$ for dithizone will be a satisfactory measure of $[HDz]_o$. This condition $pH \ll pH_{\frac{1}{2}}$ can also be expressed in the form $p_r K_r/\{H\} \ll 1$, and introducing this into equation (2), we have for the case where $V_o = V_w$:

$$[HR]_{initial} = M_{HR}/V_o = [HR]_o + n[MR_n]_o \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Provided, therefore, that no other species participate in the extraction equilibria (*q.v.*), measurements of the absorbancies of the organic phases before and after the extraction of zinc dithizonate (and the concomitant disappearance of an equivalent amount of dithizone) will permit of the determination of both $[HR]_o$ and $[MR_n]_o$ once a calibration curve has been set up.

The ideal system for quantitative verification of equation (1) demands *inter alia* a metal which forms a single dithizone complex and one which shows the least tendency to

* $T_{solution}$ (the overall rectilinear *transmittance* of an absorption cell with parallel transparent windows of, *e.g.*, glass or fused quartz, containing a solution or homogeneous mixture of solids, liquids, vapours, or gases, of which the compound of interest is the solute or one constituent) is defined as the ratio of the homogeneous radiant energy leaving the back face of the cell to that incident at right-angles upon the front face. $T_{solvent}$ is the (overall) transmittance of the same, or a duplicate, cell containing pure solvent or the same mixture in the same relative proportions minus the constituent of interest. The *transmittancy* of the sample is given by $T_s = T_{solution}/T_{solvent}$, and the *absorbancy* of the sample is defined by $A_s = -\log_{10} T_s = \log_{10}(T_{solvent}/T_{solution})$. (Cf. *Nat. Bur. Standards*, Letter Circular 1947, LC-857; Mellon, *Analyt. Chem.*, 1949, **21**, 3.)

complex with any possible component of the buffers employed. Accurate measurement of the pH of the aqueous phase contra-indicates the use of very strongly acid or very strongly alkaline media and calls for a metal complex of neither too large nor too small stability (cf. Irving and Williams, *Nature*, 1948, **162**, 746). Despite its amphoteric character (*i.e.*, its tendency to form competitive complexes with hydroxyl ions at high alkalinities) the bivalent metal zinc most completely fulfils these conditions, and equilibrium in the zinc–dithizone system should be representable by equation (1) with HR = HDz, M = Zn, and $n = 2$.

Preliminary measurements by Kolthoff and Sandell (*J. Amer. Chem. Soc.*, 1941, **63**, 1906) summarised in Table 1 show that substantially constant values are obtained for K even when the extractability is varied 100-fold and the excess of dithizone from 25% to 2000%. It has, however, been pointed out [Irving and Williams, *loc. cit.*; and cf. equation (1)] that a change of one unit in the pH of extraction has the same effect upon the percentage of metal extracted as a ten-fold change in the term $[HDz]_o$. Equation (1) could thus be subjected to a far more stringent test by studying the extractability of zinc from solutions of widely varied acidity. Such a proposal at once introduces a number of complicating factors, since changes in the composition of the aqueous phase due to the presence of buffering agents may be expected to diminish the extractability of zinc should it form competitive complexes with any of the ions present. Quite apart from such possible specific effects, secondary salt effects will affect the final position of partition equilibrium, whilst primary salt effects, and any reduction in the effective concentration of metal ions as a result of complexing, will play a part in affecting the rate at which partition equilibrium is attained.

TABLE 1.

pH	Phase ratio, H_2O : $CHCl_3$, ml.	Zn, μg.	HDz, μg.	E	K
3·05	10 : 10	11	588, 980	0·29, 0·62	4·7, 3·6
—	5 : 10	5·7	1000	0·93	5·1
3·71	7·5 : 5	5·5,[a] 5·3,[a] 4·9 [b]	150	0·93, 0·77, 0·66	3·25, 2·6, 2·3
3·97	10 : 10	10·0	100, 250, 750	0·3, 1·63, 27	3·4, 3·0, 4·5
—	—	10·5	245, 490	1·44, 7·1	2·8, 3·1

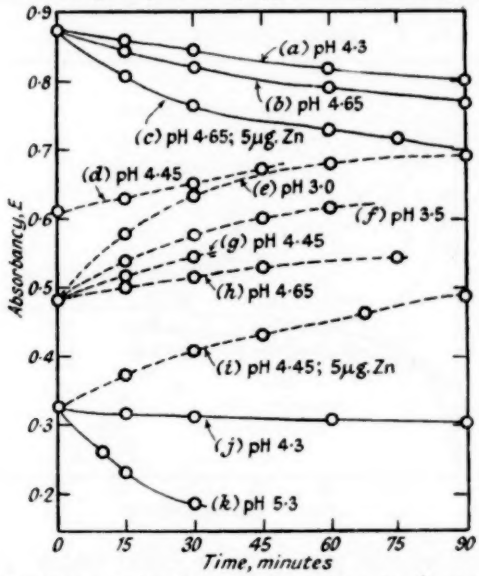
[a] Aqueous phase M with respect to $NaNO_3$. [b] Aqueous phase M with respect to NaCl.

The Attainment of Partition Equilibrium.—In published procedures for the analytical determination of zinc with dithizone, various lengths of time of shaking—generally 1 or 2 minutes—have been allowed for the attainment of partition equilibrium at that pH where the extraction is taken as being quantitative. Kolthoff and Sandell (*loc. cit.*) clearly recognised that this period might be insufficient and prescribed 2 hours for the measurements they made at pH 3—4. That still longer might be necessary at lower acidities can be inferred from data presented by Walkley (*Proc. Austral. Chem. Inst.*, 1942, **9**, 29) and discussed previously (Irving and Williams, *loc. cit.*).

It is clear that the only reliable way of establishing whether partition equilibrium has been truly and finally reached is to approach this point from both sides. We shall speak of a " forward reaction " when zinc dithizonate is formed by shaking together an aqueous buffer containing zinc ions and a solution of dithizone in an immiscible organic solvent, the complex and other species then partitioning between the two phases; the term " back reaction " will be used to describe the processes which ensue when a solution of zinc dithizonate in the organic solvent is shaken with an aqueous buffer whereby reversion takes place to a greater or less extent, zinc ions passing into the aqueous phase and dithizone appearing in the organic phase together with any remaining metal complex. Now any change in the concentration of dissolved zinc dithizonate produces a proportional change in the absorbancy of the organic phase and so permits a simple means of following the kinetics of these processes. From calibration curves (not reproduced here) it was found that the formation and quantitative extraction of 1·06 μg. of zinc (and the concomitant disappearance of the equivalent amount of dithizone) causes a decrease in absorbancy of 0·100 unit under the experimental conditions used and when working with

chloroform as a solvent (see p. 365). With carbon tetrachloride as a solvent, or when the Spekker absorptiometer was replaced by a Beckman spectrophotometer, the appropriate factor had to be used. Fig. 1 shows some typical results demonstrating (curves *a* and *b*, *j* and *k*) that the rate of the forward reaction is decreased by lowering the pH of the aqueous phase, the concentration of zinc and dithizone being constant (for each pair). At constant pH, increasing the concentration of dithizone at a fixed zinc concentration (curves *j* and *a*) or increasing the concentration of zinc ion at constant dithizone concentration (curves *b* and *c*) produces the expected increase in the rate of the forward reaction. At constant pH and zinc dithizonate concentration, increase in the concentration of excess dithizone retards the back reaction (curves *g* and *d*), but lowering the pH of the aqueous phase whilst maintaining other factors constant produces a striking increase in the rate of the back reaction (curves *e*, *f*, *g*, and *h*).

FIG. 1. *Factors affecting the rate of approach to partition equilibrium.*



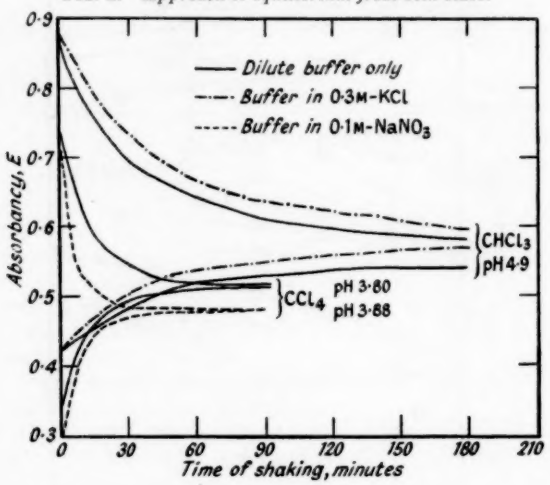
Full curves = forward reaction ; broken lines = back reaction ; 2·5 μg. of zinc present in all cases except curves (c) and (i).

It must not be overlooked that the measured rates include both interactions between molecules and ions in solution and the transfer of various species from one phase to the other. That interphase equilibration is not the only rate-determining stage follows from the influence of pH changes; but though these indicate that the concentration of dithizonate ions must play a significant rôle in determining the rate of the forward reaction, our detailed studies of the kinetics are not yet completed. However, since the partition coefficient of dithizone between water and carbon tetrachloride is greater than that between water and chloroform (Irving, Cooke, Woodger, and Williams, *loc. cit.*) there will always be a larger fraction of the total uncomplexed dithizone present in the aqueous phase as dithizonate ion when carbon tetrachloride is used than when a chloroform solution is equilibrated with an aqueous buffer of the same pH. An immediate result of this is to cause the rate of reaction to be greater when using carbon tetrachloride as a solvent for dithizone. Fig. 2 shows that reaction was incomplete in the chloroform–water system at pH 4·9 even after 3 hours' shaking. When carbon tetrachloride was used 1½ hours or even less sufficed to reach equilibrium even at the lower pH of 3·8, and with a smaller concentration of dithizone : at pH 4·9 the reaction is complete within a few minutes.

When, as in most of the measurements with carbon tetrachloride, the curves for the forward and the back reaction actually coincided after a certain time of shaking, the attainment, of equilibrium was not in doubt. In measurements with chloroform, shaking was always continued for long enough to establish the course of the rate curves, and the position of ultimate equilibrium was established by interpolation if necessary; but no results were accepted where the absorbancies of the organic phases in the forward and back reactions differed by more than 5%.

Fig. 2 shows that the effect of a fairly high concentration of chloride ions is to decrease the rate of the forward reaction and to increase that of the back reaction. There is also a change in the final position of equilibrium, the percentage of zinc extracted being reduced from 72·5 to 65%. These effects could well be attributed to the known tendency of zinc ions to form complexes with chloride ions. But caution is necessary in interpreting both such rate and equilibrium measurements, for the presence of a moderate concentration of even an indifferent electrolyte such as sodium nitrate changes the rates

FIG. 2. *Approach to equilibrium from both sides.*



of at least the forward reaction (Fig. 2) to an extent greater than can be explained by the small variation in pH and reagent concentration. Here the percentage of zinc extracted happened to be 57% in both cases, so that the effect of the sodium nitrate has been to reduce the effective extraction constant, K, from 98 to 60 (p. 368).

It will be obvious from the foregoing that any attempts to correlate and interpret variations of the percentage of zinc extracted with change of pH can only be justified with data obtained at equilibrium and with due regard to the composition of the buffers employed. Entirely misleading pictures would be obtained, if, *e.g.*, measurements with

TABLE 2. *The effect of chloride and phosphate ions upon the extractability of zinc from phosphate buffers at* pH 6·7.

Zinc taken, μg.	4	8	12	16	20
KCl, M	0·2	0·4	0·6	0·8	1·0
Zn, %, extracted in 2 min. from					
(*a*) M-Na_2HPO_4	20	19	14	13	10
(*b*) 0·1M-Na_2HPO_4	48	46	47	45	40

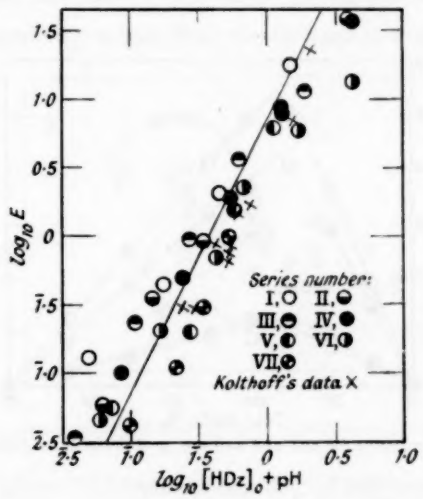
chloroform solutions of dithizone were made after only 15 minutes' shaking. Nevertheless, data obtained after even 2 minutes' shaking and shown in Table 2 confirm the effect of chloride ion in reducing at least the *rate* of extraction of zinc and demonstrate the even greater effect of phosphate ions and the advisability of omitting them from buffer

mixtures used in measurements of the extractability constant K: but these data are valueless as indicating the possible position of extraction equilibrium.

A study was next undertaken of the effect of pH upon the equilibrium percentage of zinc extracted by dithizone solutions of the same initial strength from aqueous buffers of different composition. Of the family of curves which resulted, that obtained for M/200 phthalate buffers formed the left-hand member, indicating the greatest extent of extraction at any pH and the least degree of complexing with zinc ions. To its right lay curves for M/10- and M/2-phthalate, and M/2-acetate, -tartrate, and -citrate in that order: at any given pH more zinc was extracted from an acetate buffer than from a phosphate buffer of the same molarity.

The Extraction Constant for the Zinc–Dithizone–Chloroform System.—In this main part of the work the position of equilibrium was determined for a variety of acidities and varying values of $[HDz]_o$. The same total weight of zinc (5 μg.) was present in each case and

FIG. 3. *Equilibrium data obtained from the extraction of zinc by solutions of dithizone in chloroform.*



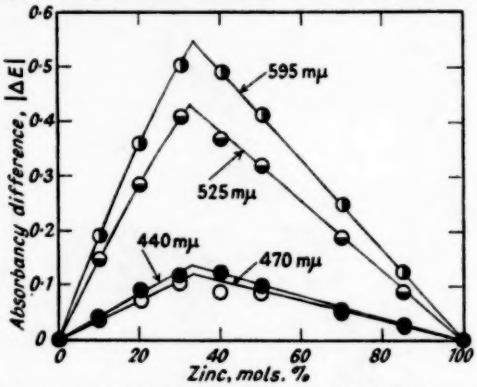
M/200-phthalate buffers were employed throughout, equilibrium being approached as usual from both sides. In the first series of experiments the total amount of dithizone in the system amounted to 160 μg., and this was progressively reduced to 146, 90, 70, 60, 48, 32, and 15 μg. in Series II to VIII. In Series VII and VIII the initial concentration of dithizone was insufficient to react with all the zinc taken (5 μg. of Zn ≡ 40·3 μg. of HDz) so that complete extraction could never be achieved. Furthermore, equilibrium could not be approached by the back reaction; but even without this criterion the low percentage of zinc extracted showed that partition equilibrium was not being reached even after 4—5 hours' shaking. The possibility of the formation of a water-soluble zinc–dithizone complex (*q.v.*) should also be taken into account.

Series I to VI at once provide sets of values of the parameters E, pH, and $[HDz]_o$ which can be used to test equation (1*a*). Fig. 3 shows experimental values of $\log_{10} E$ plotted against $\log_{10}[HDz]_o$ + pH, together with a straight line of slope $n = 2$ corresponding to a complex of formula $ZnDz_2$. The radius of the circles is not intended to indicate the precision of the measurements, which falls off very rapidly as the percentage of extraction falls outside the range 50 to 95%. Agreement with theory is satisfactory in view of the range of extractabilities and acidities covered, and the scatter is least, as might be expected, in the neighbourhood of $\log_{10} E = 1$ (50% extraction). Values obtained by Kolthoff and Sandell (*loc. cit.*) are indicated by crosses in Fig. 3, and the fact that they all correspond to lower extractabilities than we have found might possibly be attributable to equilibrium

not having been attained, although the fact that they were obtained with buffers of different and higher salt content must not be overlooked (cf. p. 358). The greater self-consistency of their measurements is due in large part to the limited range (pH 3·05—3·97) covered. If we accept the formula of the complex as $ZnDz_2$ we obtain $K = 8 \pm 0{\cdot}8\%$ from our data, which may be compared with the average value $3{\cdot}3 \pm 0{\cdot}3\%$ obtained if equal weight is given to all Kolthoff and Sandell's values. On the other hand, the data of Fig. 3 could justifiably be considered as conforming more satisfactorily with a line of slope as low as 1·7 though an objective estimate of the position of this " best straight line " is difficult in view of the low precision of data corresponding to high and low values of $\log_{10} E$.

There can, however, be little doubt as to the formula of the red zinc–dithizone complex which is extracted into the organic phase. That the pure solid conforms to the expected composition is shown by Fischer's analysis (*Annalen*, 1882, **212**, 316) and those of our own specimens. The formula is supported by measurements incidental to setting up calibration curves (p. 365), and is finally established by a spectrophotometric study of mixtures of zinc and dithizone in a monophase of chloroform, alcohol, and water, using the method

FIG. 4. *The formula of zinc dithizonate—Job's method of continuous variations.*



(*Values of* ΔE *are negative for* 595 *and* 440 *mμ, and positive for* 525 *and* 470 *mμ.*)

of continuous variations described by Job and modified by Vosburg and Cooper (*J. Amer. Chem. Soc.*, 1941, **63**, 437). The ordinates in Fig. 4 measure the difference, ΔE, at each of four selected wave-lengths, between the measured absorbancy and that calculated on the assumption that no complex formation has taken place. This difference reaches its maximum value when the mole-fraction is 0·33 corresponding to a molecular ratio Zn : HDz of 1 : 2. No other absorbing species appear to be formed under these experimental conditions.

Even though the formula, $ZnDz_2$, of the extracted species is no longer in doubt, a non-integral slope for the plot of $\log E$ against $\log [HDz]_o + pH$ (Fig. 3) could nevertheless arise from the following considerations. If we accept the current view that the formation of a complex proceeds through the stepwise addition of ligands, we must extend our treatment of the fundamental equilibrium to include the following species in the aqueous phase : $Zn^{++} + Dz^- \rightleftharpoons ZnDz^+$; $ZnDz^+ + Dz^- \rightleftharpoons ZnDz_2$. These equilibria are governed by stability constants defined by $k_1 = [ZnDz^+]/[Zn^{++}][Dz^-]$ and $k_2 = [ZnDz_2]/[ZnDz^+][Dz^-]$, whilst the amphoteric character of the zinc ion can be considered in terms of the stability constants $k_n^h = [Zn(OH)_n]/[Zn(OH)_{n-1}][OH^-]$. We can now write (deferring consideration of activity coefficients for the time being)

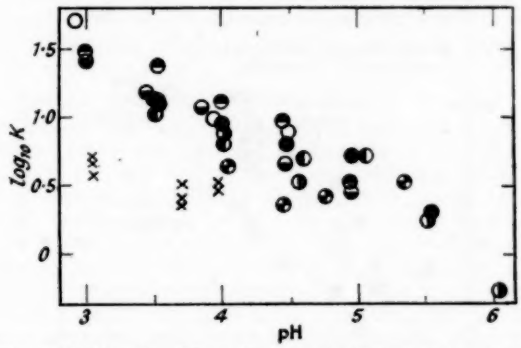
$$\begin{aligned} E &= [ZnDz_2]_o/([Zn^{++}]_w + [ZnDz^+]_w + [ZnDz_2]_w + [ZnOH^+]_w^+ \ldots .) \\ &= ([ZnDz]_o/[Zn^{++}]_w)/(1 + k_1[Dz^-] + k_1k_2[Dz^-]^2 + k_1^h[OH^-] \ldots) \\ &= \frac{K[HDz]_o^2}{\{H\}^2}\Big/\left(1 + k_1p_rK_r\frac{[HDz]_o}{\{H\}} + k_1k_2p_r^2K_r^2\frac{[HDz]_o^2}{\{H\}^2} + \frac{k_1^hK_w}{\{H\}} + \text{etc.}\right) \end{aligned}$$

Taking logarithms and rearranging, we have

$$\log_{10} K \text{ (calc.)} = \log_{10} E\text{(expt.)} - 2(\log_{10}[\text{HDz}]_o + \text{pH})$$
$$= \log_{10} K - \log_{10}(1 + k_1 ax + k_1 k_2 a^2 x^2 + k_1{}^h K_w/\{\text{H}\} + \text{etc.}) \quad (4)$$

where the variable $x = [\text{HDz}]_o/\{\text{H}\}$, and the constant a is given by $\log_{10} a = \log_{10} p_r K_r = \text{pH}_{\frac{1}{2}}$. It follows that the value of the extraction constant calculated according to equation (1) may, depending on the values of k_1, k_2 and $k_n{}^h$ (*i.e.*, on the extent to which water-soluble complexes participate in the equilibria), be found to vary with the terms $[\text{HDz}]_o$ and pH—in short with the conditions of extraction. In our experiments the latter parameter was subject to the greater variation, and, as may be inferred from equation (4), the calculated extraction constants would then decrease with increasing pH. This prediction agrees with the trend of our experimental data shown plotted against pH in Fig. 5; the trend of Kolthoff and Sandell's value is in the same direction but the agreement must not be over-emphasised in view of the small range of acidities they cover. If we insert numerical values for $p_r K_r$ ($2{\cdot}63 \times 10^{-11}$; Irving *et al.*, *loc. cit.*)

FIG. 5. *The variation of* $\log_{10} K$ *for chloroform with* pH.



(*The symbols employed have the same significance as in Fig.* 3.)

and $k_1{}^h K_w$ ($2{\cdot}45 \times 10^{-10}$; Latimer, "Oxidation Potentials," New York, 1938) into equation (4), it is obvious that the hydrolysis of the zinc ion to give $ZnOH^+$ is not sufficiently extensive over the range of acidities studied to explain the trend of our results, and it proved impossible to assign consistent values to k_1 and k_2 though the former appeared to lie in the range $10^{10} < k < 10^{12}$.

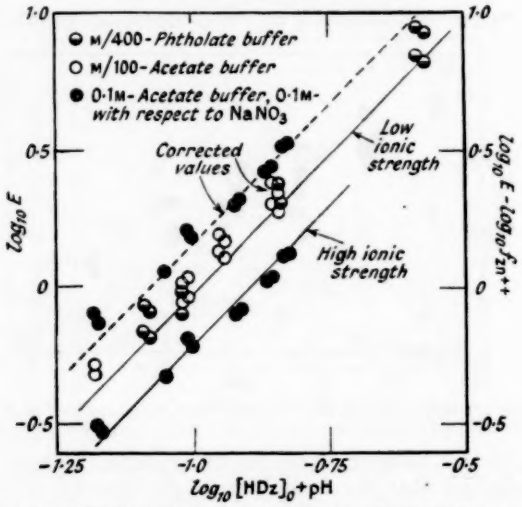
The Extraction Constant for the Zinc–Dithizone–Carbon Tetrachloride System.—Since the factor $a = p_r K_r$ for carbon tetrachloride is some 50 times greater than that for chloroform, we should expect a larger dependence of the experimental values of the extraction constant K upon the conditions of measurement. An additional reason for studying this system is provided by Buch's data (*Finska Kemist. Medd.*, 1944, **53**, 25) for the extraction of zinc from acetate buffers from which Sandell (*loc. cit.*) calculates $K_{\text{OCl}_4} = 4$, a value almost identical with that found by him in chloroform (see p. 358). This is most surprising in view of the known dependence of K upon parameters characteristic of the solvent, and it conflicts with the fact that the optimum pH for the extraction of a metal with a solution of dithizone in carbon tetrachloride appears without exception to lie below that of the corresponding value for chloroform.

Although preliminary measurements had shown that equilibrium was attained more rapidly when carbon tetrachloride was substituted for chloroform (see p. 359 and Fig. 2), partition equilibrium was nevertheless invariably approached from both sides and, in view of the reduced precision of measurements at high or low values of E, the percentage of zinc extracted was kept within the range 20—90%. Excellent agreement was obtained between preliminary measurements where the forward and back reactions were investigated

in separate experiments (p. 368), but in the final measurements both forward and back reactions were conducted simultaneously. The variation with pH of the percentage of zinc extracted was found to be the same whether the aqueous buffer was M/200-phthalate or M/100-acetic acid–sodium acetate, and Fig. 6 shows the plot of log E against log $[HDz]_o$ + pH together with a line of slope 2. The agreement with theory is most satisfactory, and we find $K = 97 \pm 2$. When these buffers of low ionic strength are replaced by one for which $\mu \sim 0{\cdot}1$ due to a constant background of 0·1M-sodium nitrate, the data, though conforming excellently to a line of slope 2 (Fig. 6) now lead to the value $K = 66 \pm 2$. Despite the apparent disagreement, there is no doubt that K_{CCl_4} is greater than K_{CHCl_3} by a factor of about 10; this is compatible with qualitative observations but in marked disagreement with Buch's earlier data.

If, however, the derivation of equation (1) is carried through by using activities in place of concentration terms, and thermodynamic constants denoted by adding the

FIG. 6. *The effect of ionic strength upon the extraction constant for the system zinc–dithizone–carbon tetrachloride and water.*



(*The right-hand ordinate scale applies to the broken line.*)

superscript T to symbols previously used, then, by making the appropriate redefinitions where necessary, it can readily be shown that

$$E = K^T f_{Zn^{++}} \{HDz\}^2/\{H\}^2$$

or
$$\log_{10} E - \log_{10} f_{Zn^{++}} = \log_{10} K^T + 2(\log_{10} \{HDz\}_o + pH) \quad . \quad . \quad . \quad (5)$$

where $f_{Zn^{++}}$ is the activity coefficient of the zinc ion and $K^T = (p_r{}^T K_r{}^T)^2/(p_e{}^T K_e{}^T)$. On assuming that $[HDz]_o = \{HDz\}_o$, and that $f_{Zn^{++}}$ equals $f_\pm$, the mean activity coefficient for zinc sulphate, and making the appropriate calculations, all the partition data now conform to a single line of slope 2 (Fig. 6, broken line). In effect, points corresponding to media of low ionic strength are displaced vertically upwards by 0·05 to 0·1 logarithmic unit, whilst those for the medium of high ionic strength need correction to a much greater extent of 0·4 unit on the $\log_{10} E$ scale. From the intercept at $\log_{10} E = 0$, we have $\log_{10} K^T = 2{\cdot}11 \pm 0{\cdot}01$, or $K_{CCl_4} = 130$ ($\mu = 0$) with a standard deviation of ± 4.

The work with carbon tetrachloride was not pursued with buffers of pH > 4 where materially lower concentrations of dithizone would have had to be used to keep within a convenient range of extractabilities; but over the admittedly limited range explored there is not the slightest evidence of any trend in the values of K with increasing pH such

as had been noted in the chloroform system. In this system Kolthoff and Sandell used "biphthalate buffers, of pH 3 and 4, according to Clark and Lubs." Assuming these to have been 0·05M, we can estimate the value $K_{CHCl_3} = 9$ ($\mu = 0$), which compares very favourably with the value $K^T = 11$ obtained by applying the appropriate activity correction to our data at the same pH. Since, as a result of increasing ionisation, the ionic strength of our phthalate buffers increased as the pH was increased, the activity correction to be applied to the data at high pH values becomes increasingly significant, and it may well be that this accounts for the major part, if not the whole, of the drift of values shown in Fig. 5. Unfortunately, the exact composition of these buffers (which were prepared by addition of arbitrary amounts of alkali to stock dilute phthalate buffer—the measurement of pH being deferred until after partition equilibrium had been attained) is not available, and we cannot now subject this hypothesis to a quantitative test. There now remains, however, no very definite evidence for the existence of a water-soluble complex such as $ZnDz^+$, and although further progress could be made by more precise equilibrium studies of extraction from media of accurately known ionic strength, it is clearly desirable to refine the analytical methods available for determining the concentration of the various species comprising the equilibrium mixtures. Particularly valuable information would result from an objective determination of the amount of dithizone present as the species HDz, Dz^-, $ZnDz^+$, and $ZnDz_2$ in the *aqueous* phase, and to this end the synthesis of a radioactive reagent with suitably labelled atoms has been undertaken.

Experimental

Materials and Technique.—Precautions customary in work with dithizone were scrupulously observed. All solvents, buffers, reagents, and glassware were freed from trace metals in the customary way (*J.*, 1949, 537, 541, 1847). Partition equilibrium was approached by shaking organic and inorganic solutions in 125-ml. Pyrex stoppered funnels in the earlier work with chloroform, but with carbon tetrachloride stoppered Pyrex test-tubes were employed exclusively and phase separation was assisted if necessary by centrifugation.

The Standard Mixed-colour Calibration Curves for Zinc Dithizonate.—Mixtures of x ml. of zinc solution (1 μg. per ml. of acetate buffer) with $(10 - x)$ ml. of an acetate buffer of pH 7·5, both saturated with chloroform, were shaken for 5 minutes with a solution of dithizone in chloroform previously saturated with water by equilibration with 0·1N-hydrochloric acid. After standing to permit of phase separation the organic layer was separated through a plug of cotton wool (previously freed from trace-metals) and after rejection of the first portions it was used to fill a 1-cm. cell of a Spekker absorptiometer which had been warmed slightly on the lamp-house to avoid any danger of spurious high absorbancies resulting from the separation of water droplets had the organic phase become supersaturated following a drop in temperature after equilibration. The absorbancy (optical density) of the initial dithizone solution, E_o, and that of each mixture of zinc dithizonate and excess dithizone, E_m, was measured by use of the tungsten lamp and Ilford orange filter No. 607. The plot of absorbancy against the weight of zinc taken was linear over the range 0—6 μg., the extraction of 1 μg. of zinc corresponding to a decrease in absorbancy of $0{\cdot}094_5$. From previous work (Irving, Risdon, and Andrew, *J.*, 1949, 537) on the relation between absorbancy and the concentration of chloroform solutions under these conditions, we calculate that 7·2 μg. of zinc have reacted with 57 μg. of dithizone, corresponding to a molecular ratio Zn : HDz = 1 : 1·97. The calibration curve for zinc with solutions of dithizone in carbon tetrachloride was carried out by use of an 0·05M-acetate buffer of pH 5·33, and 30 minutes' shaking. The following data are typical, but fresh calibration curves were repeated at intervals to check the purity of the dithizone used and to ensure that there had been no deterioration or change in the transmittancy of the optical filter.

Zn taken, μg.	0	1·0	1·5	2·0	3·0	4·0	5·0	6·0
E_m	0·665	0·570	0·535	0·488	0·403	0·318	0·245	0·150

On the average 1 μg. of zinc reduces the absorbancy by 0·085 unit, indicating for the dissolved species the formula $ZnDz_{2\cdot04}$.

Kinetic and Equilibrium Studies.—"Forward" reactions were studied by shaking aqueous buffers containing known amounts of zinc with dithizone solutions of known initial concentration (as measured by E_o) for the desired length of time. After separation of the phases, the pH of the aqueous phase was measured with a Cambridge pH-meter, and the

absorbancy of the organic phase determined as above. The concentration of excess dithizone, $[HDz]_o$, is proportional to E_m, whilst the amount of zinc extracted is obtained from $E_o - E_m$ and the factor obtainable from the calibration curves. "Back" reaction mixtures were prepared by extracting known amounts of zinc quantitatively from aqueous solution under the conditions used for preparing the calibration curves (see above). The initial composition in terms of $[ZnDz_2]$ and $[HDz]_o$ followed from the amount of zinc and dithizone taken, but it was invariably checked by measurements of the changes in absorbancy and sometimes by a complete reversion of the metal complex by prolonged shaking with 0·1M-hydrochloric acid. Equilibration was carried out on a mechanical shaker operating at 150 cycles per minute, and in kinetic measurements a number of identical mixtures were made up and set shaking simultaneously, one test-tube (or funnel) being removed at suitable intervals for the analysis of its contents. The temperature was 25° ± 3°. Blanks were run in every case.

Factors Affecting the Rate of Approach to Equilibrium in the System Zinc–Dithizone–Water and Chloroform.—The values of E_m obtained in some typical experiments are given below. (All measurements with chloroform solutions were carried out by R. J. P. W.)

Expt. No.	pH	Time, min.:	0	15	30	60	90	150
1	4·30		0·325	—	0·315	0·310	0·305	—
2	4·30		0·870	—	0·845	0·820	0·800	—
3	4·65		0·870	—	0·820	0·790	0·765	—
4	5·30		0·325	0·215	0·180	—	—	—
5	4·65		3·75	3·59	3·56	—	—	—
6	4·60		0·750	0·680	0·645	0·615	0·590	0·570
7	3·00		0·480	0·585	0·635	0·680	0·695	—
8	3·50		0·480	0·540	0·575	0·615	—	—
9	4·65		0·480	0·498	0·515	0·540	—	—
10	4·45		0·30	0·35	0·38	0·43	0·47	0·51
11	4·45		0·48	0·515	0·545	—	—	—
12	4·45		0·110	0·130	0·150	0·170	—	—

The amount of zinc taken (as zinc ion or zinc dithizonate) was 2·5 μg. in all experiments save Nos. 6 and 10, where 5·0 μg. were used; Nos. 1—6 are forward, Nos. 7—12 are back reactions. The organic phase of experiment No. 5 was diluted 5-fold before measurement of absorbancy.

The Effect of Potassium Chloride upon the Rate of Extraction of Zinc.—A mixture of 2 ml. of zinc sulphate solution (4·8 μg. Zn), 3 ml. of M-potassium chloride (or distilled water), and 5 ml. of 0·004M-phthalate buffer of pH 4·9 was shaken for varying lengths of time with 10 ml. of a solution of dithizone in chloroform ($E_o = 0·875$). Simultaneous measurements were made of the rate of reversion of 10 ml. of zinc dithizonate–dithizone mixtures in chloroform (containing the same total amount of zinc and dithizone as above) on shaking with an aqueous phase containing 2 ml. of water in place of the zinc solution.

	No KCl present					0·3M-KCl present				
Time, min.	0	30	60	90	180	0	30	60	90	180
Zn, % extracted:										
(i) Forward reaction	0	14	52	59	71	0	32	47	52	62
(ii) Back reaction	100	86	79	78	74	100	83	75	73	68

The Effect of Potassium Chloride on the Position of Equilibrium.—Similar measurements were carried out at different acidities, the pH of the phthalate buffers being adjusted to the desired values by the addition of 0·02M-hydrochloric acid (or ammonia); $E_o = 0·738$.

pH	1·8	3·5	4·0	4·6	4·9	5·5	6·5
Zn, %, extracted:							
(i) No KCl	0	6	8	40	66	91	100
(ii) 0·3M-KCl	0	8	18	58	78	96	100

The Effect of Potassium Chloride on the Rate of Reaction in Phosphate Buffers.—In order to see whether the effect of potassium chloride and phosphate ions on the extraction of zinc was due to specific complexing and/or to an activity effect it was necessary to produce buffers of the same pH but widely different concentration. Solutions of 1·0M- and 0·1M-disodium hydrogen phosphate were prepared, together with similar buffers which were M with respect to potassium chloride and contained 2μg./ml. of zinc. By adding drops of 1·0M-hydrochloric acid, the

pH was adjusted empirically to the value 6·70 in each case, the four buffer solutions now having the following composition (in addition to the above small volume of acid) :

	Concn. of Na_2HPO_4, M	Concn. of KCl, M	Zn, μg./ml.		Concn. of Na_2HPO_4, M	Concn. of KCl, M	Zn, μg./ml.
(i)	1	0	0	(iii)	0·1	0	0
(ii)	1	1	2	(iv)	0·1	1	2

Mixtures of x ml. of (i) with $(10 - x)$ ml. of (ii) contained varying amounts of potassium chloride in M-disodium hydrogen phosphate buffers of pH 6·7. These and similar mixtures solutions (iii) and (iv) were shaken for two minutes only with an equal volume of dithizone solution of $E_o = 0{\cdot}831$. The results are shown in Table 2 (p. 360).

The Extraction Constant for the Zinc–Dithizone–Chloroform System.—Preliminary experiments having indicated the time necessary to reach equilibrium, simultaneous measurements were made of the forward and back reactions with mixtures so designed that at equilibrium both organic and both aqueous phases should be identical in composition in the two cases. If the two values of E_m differed by more than 5% the experiment was repeated with a longer time of shaking. When a very high concentration of dithizone was used (Series I) the absorbancy was too high for direct measurement, and after equilibrium had been attained the zinc dithizonate in the organic layer was " reverted " into 10 ml. of 1M-hydrochloric acid and after neutralisation and buffering to pH 8·0 determined in the usual way. In Series VII and VIII the amount of dithizone taken was less than that sufficient to combine with all the zinc. No equivalent mixture could thus be made up for the back reaction and the data given refer only to the forward reaction.

Factors Affecting the Rate of Approach to Equilibrium in the System Zinc–Dithizone–Carbon Tetrachloride–Water.—All measurements with carbon tetrachloride solutions were carried out by C.F.B., stoppered test-tubes being used exclusively in preference to separating funnels. The extent to which concentration changes occurred during long periods of shaking was investigating by taking a mixture of at least 10 ml. of water and a similar volume of carbon tetrachloride and placing it in a Pyrex test-tube (20 × 3 cm.) with a B 24 ground-in stopper. The tube was stoppered and weighed after being shaken for 0, ½, 1½, and 4 hours on a Kahn shaking machine at 150 cycles per minute. With nine different tubes the largest decrease in the weight of liquid after 4 hours was 0·1% and the average loss was only 0·002%.

Series No.	pH	$\log_{10}[HDz]_o$	$\log_{10} E$	$\log_{10} K$	Series No.	pH	$\log_{10}[HDz]_o$	$\log_{10} E$	$\log_{10} K$
I	2·58	$\bar{5}$·7943	$\bar{2}$·0044	1·27	V	2·47	$\bar{5}$·3663	$\bar{2}$·1522	2·47
	2·93	$\bar{5}$·7830	$\bar{1}$·1264	1·70		3·50	$\bar{5}$·3552	$\bar{3}$·7392	1·03
	3·50	$\bar{5}$·7608	$\bar{1}$·6526	1·13		4·02	$\bar{5}$·2908	$\bar{1}$·4324	0·81
	3·95	$\bar{5}$·7157	0·3174	0·99		4·60	$\bar{5}$·1481	0·2071	0·71
	4·50	$\bar{5}$·6782	1·2520	0·90		5·05	$\bar{6}$·9990	0·8067	0·72
	5·00	$\bar{5}$·6710	>3·0	—					
					VI	3·52	$\bar{5}$·2546	$\bar{2}$·6630	1·10
II	2·53	$\bar{5}$·7582	<$\bar{3}$·0	—		4·02	$\bar{5}$·2046	$\bar{1}$·3265	0·88
	3·00	$\bar{5}$·7471	$\bar{2}$·8090	1·41		4·58	$\bar{5}$·0689	$\bar{1}$·8347	0·54
	3·45	$\bar{5}$·7253	$\bar{1}$·5229	1·18		4·96	$\bar{6}$·8928	0·3680	0·67
	3·85	$\bar{5}$·6956	$\bar{1}$·9513	0·86		5·52	$\bar{6}$·7379	0·7812	0·26
	4·48	$\bar{5}$·6371	0·8862	0·65		6·03	$\bar{6}$·6332	1·1167	$\bar{1}$·79
	4·96	$\bar{5}$·6212	1·5911	0·43					
					VII	4·05	$\bar{6}$·9342	$\bar{3}$·6232	0·65
III	2·53	$\bar{5}$·5436	$\bar{2}$·1023	1·96		4·45	$\bar{6}$·8928	$\bar{1}$·0458	0·36
	3·00	$\bar{5}$·5387	$\bar{2}$·5906	1·51		4·76	$\bar{6}$·7679	$\bar{1}$·4777	0·42
	3·52	$\bar{5}$·5056	$\bar{1}$·3979	1·35		5·35	$\bar{6}$·3700	$\bar{1}$·9948	0·56
	4·00	$\bar{5}$·4369	0·0000	1·13		5·98	7·5908	0·2432	1·10
	4·45	$\bar{5}$·3552	0·6021	0·99					
	4·96	$\bar{5}$·3161	1·0910	0·54	VIII	4·20	$\bar{6}$·7379	$\bar{3}$·1822	0·31
						5·10	$\bar{6}$·4369	$\bar{1}$·2989	0·22
IV	3·52	$\bar{5}$·4113	$\bar{2}$·9899	1·13		5·80	$\bar{6}$·2046	$\bar{1}$·5324	$\bar{1}$·51
	4·03	$\bar{5}$·3515	$\bar{1}$·6944	0·93		6·15	$\bar{6}$·0689	$\bar{1}$·5941	$\bar{1}$·15
	4·48	$\bar{5}$·2546	0·2900	0·82		7·00	*	$\bar{1}$·6990	—
	4·96	$\bar{5}$·1481	0·9495	0·73					
	5·52	$\bar{5}$·1103	1·5736	0·31					

* Indicates that there was no measurable excess of dithizone.

The Effect of Change of Ionic Strength on the Rate of Extraction of Zinc.—In Series A, mixtures of 1 ml. of stock zinc sulphate solution (5 μg. of Zn/ml.), 2 ml. of 0·5M-sodium nitrate, 5 ml. 0·2M-acetic acid–sodium acetate buffer of pH 3·88, and 2 ml. of metal-free water were shaken

with 10 ml. of a solution of dithizone in carbon tetrachloride of $E_0 = 0{\cdot}735$ when studying the forward reaction. For the back reaction 10 ml. of a solution of zinc dithizonate in carbon tetrachloride (5 μg. of Zn) were shaken with 2 ml. of 0·5M-sodium nitrate, 5 ml. of 0·2M-buffer, and 3 ml. of water. In Series B the aqueous phase was in each case a 0·02M-acetic acid–sodium acetate buffer of pH 3·80, containing 5 μg. of Zn for the forward reaction only; $E_0 = 0{\cdot}750$. The results are plotted in Fig. 2.

Time of shaking, min.		0	10	20	60	90
Zn, %, extracted :						
Series A :	(i) forward	0	48	55	57	57
	(ii) backward	100	68	60	58	57
Series B :	(i) forward	0	40	50	54	56
	(ii) backward	100	71	62	60	58

The Extraction Constant for the Zinc–Dithizone–Chloroform System.—A set of equilibration experiments at various pH values was carried out by using aqueous phases of " high " ionic strength of the composition used in Series A above. The forward and the back reactions were studied in random order and with different samples of reagents. The following results indicate the degree of concordance obtainable in such measurements :

	Zn extracted, % :			
pH	forward	backward	$\log_{10} E$	$\log_{10}$ [HDz]$_o$
3·56	—	32·4	−0·319	−4·68
3·65	—	40·9	−0·168	−4·68
3·86	53·3, 54·0	—	0·064	−4·76
3·88	—	56·7	0·117	−4·77
3·96	—	62·4	0·220	−4·78
4·06	73·1, 72·1	—	0·423	−4·82
4·22	81·9, 80·2	—	0·630	−4·87

The definitive experiments were carried out with mixtures for forward and back reaction being equilibrated simultaneously. In Series C the aqueous phase comprised 0·1M-acetic acid–sodium acetate buffers made 0·1M with respect to sodium nitrate; in Series D it was 0·02M-acetic acid–acetate buffer; and in Series E it was a 0·0025M-phthalate buffer.

		Forward reaction			Backward reaction		
	pH	$-\log_{10} E$	$-\log_{10}$ [HDz]$_o$	$-\log_{10} f_{Zn^{++}}$	$-\log_{10} E$	$-\log_{10}$ [HDz]$_o$	$-\log_{10} f_{Zn^{++}}$
Series C	3·47	0·502	4·65	0·391	0·530	4·64	0·391
	3·62	0·33	4·67	0·393	0·33	4·67	0·393
	3·69	0·19	4·70	0·395	0·22	4·69	0·395
	3·80	0·10	4·72	0·398	0·09	4·71	0·398
	3·88	−0·02	4·74	0·400	−0·04	4·73	0·400
	3·93	−0·11	4·76	0·404	−0·12	4·75	0·404
Series D	3·50	0·33	3·78	0·05	0·33	3·78	0·05
	3·72	0·04	3·74	0·06	0·05	3·72	0·05
	3·82	−0·12	4·01	0·07	−0·10	3·99	0·07
	3·96	−0·31	4·34	0·07	−0·27	4·30	0·07
Series E	3·60	0·160	4·69	0·095	0·188	4·68	0·098
	3·68	0·084	4·70	0·094	0·090	4·70	0·101
	3·94	−0·277	4·78	0·093	−0·269	4·78	0·101
	4·28	−0·845	4·87	0·095	−0·827	4·85	0·103

Spectrophotometric Studies on the Composition of the Zinc–Dithizone Complex.—Measurements had to be made in a homogeneous phase in which zinc salts, dithizone, and zinc dithizonate were all freely soluble, and a monophase composed of 20% chloroform, 10% water, and 70% ethyl alcohol was found to be most suitable. In this medium the absorption spectrum of dithizone differs little from that in chloroform alone save that the maxima are located at 595 mμ (principal) and 440 mμ (subsidiary). Zinc dithizonate gave a single band centred at 525 mμ, and dithizonate ions (obtained by adding alkali to the monophase) had $\lambda_{max.} = 470$ mμ. These and the following measurements were made with a Beckman Model D.U. Spectrophotometer and 1·00-cm. Corex cells.

A strong solution of pure dithizone in chloroform was next prepared and its concentration found to be $1{\cdot}17 \times 10^{-4}$M by measuring the absorbancy after 5-fold dilution with pure chloroform and interpolating from a standard curve. A solution of zinc ions of exactly twice this

concentration was then prepared by diluting a suitable volume of a concentrated stock solution of zinc sulphate with M/200-phthalate buffer, the pH being adjusted simultaneously to 5·7—5·8. The mixtures required for Job's method (*loc. cit.*), in which the relative proportions of zinc and dithizone vary but the same *total* concentration in the monophase of $2{\cdot}34 \times 10^{-5}$M is maintained, were prepared by mixing $(20 - 2x)$ ml. of dithizone solution, $2x$ ml. of pure chloroform, $(10 - x)$ ml. of aqueous M/200-phthalate buffer of pH 5·7—5·8, and x ml. of the standard $2{\cdot}34 \times 10^{-4}$M-zinc solution. Absorbancies measured at four wave-lengths are given below:

	Absorbancy, measured at mμ.					Absorbancy, measured at mμ.			
x, ml.	440	470	525	595	x, ml.	440	470	525	595
0·0	0·362	0·285	0·260	0·850	5·0	0·085	0·230	0·450	0·011
1·0	0·286	0·293	0·380	0·575	7·0	0·055	0·140	0·268	0·007
2·0	0·200	0·298	0·492	0·318	8·5	0·025	0·067	0·130	0·003
3·0	0·137	0·304	0·593	0·090	10·0	0·000	0·000	0·000	0·001
4·0	0·097	0·260	0·525	0·020					

Final optical densities were established almost instantaneously in the monophase so that complex formation is clearly greatly accelerated under these conditions.

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73. *The Constitution of Yeast Ribonucleic Acid. Part XV.* The Mode of Union of the Nucleotides.*

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Yeast ribonucleic acid has been methylated by a method which is believed to avoid degradation of the molecule. From the behaviour of related nucleosides towards the methylating agent it is concluded that the extent of methylation of the carbohydrate groups is in agreement with the existence of internucleotide linkages between ribose and phosphoryl residues. Positive evidence for this has been previously lacking. After hydrolysis of the methylated polynucleotide, ribose, monomethyl ribose, and dimethyl ribose have been identified by paper chromatography in quantities which indicate a high degree of branching of the polynucleotide chain. At the sites of branching, ribose residues are believed to be triply phosphorylated, and in the terminal nucleotides of branches, they are singly esterified.

IT has long been established that the nucleotides which constitute the yeast ribonucleic acid molecule are joined together through linkages involving the phosphoric acid residue of one nucleotide and a functional group of the next (for a discussion of the earlier literature, see Tipson, *Adv. Carbohydrate Chem.*, 1945, **1**, 193). No positive evidence has been obtained, however, regarding the nature of these functional groups concerned in the internucleotide linkages although it is known that they are not phosphoric acid residues (*i.e.*, the internucleotide linkage is not a pyrophosphoric ester grouping) and it is unlikely that amino- or enolic hydroxyl groups of the nitrogenous residues are the points of attachment, since they have been shown by electrometric titration to be unsubstituted (Levene and Simms, *J. Biol. Chem.*, 1926, **70**, 327; Fletcher, Gulland, and Jordan, *J.*, 1944, 33). Furthermore, destruction of the primary amino-groups causes no reduction in molecular weight (Fletcher, Gulland, Jordan, and Dibben, *J.*, 1944, 30). These facts have led to the acceptance of the assumption (Levene and Simms, *loc. cit.*) that the phosphoric acid residue of one nucleotide is esterified with a carbohydrate hydroxyl group of the next.

The only carbohydrate phosphoric ester linkages which can be said, with any degree of certainty, to exist in the polynucleotide are those which survive hydrolysis to simple

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nucleotides. It is now known that yeast ribonucleic acid can yield mixtures of isomeric nucleotides (Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 2811; Loring, Luthy, Bortner, and Levy, *ibid.*, p. 2811; Lipkin and McElheny, *ibid.*, p. 2287), which, in spite of some evidence to the contrary (Doherty, Abstr. Papers, 118th Meeting, Amer. Chem. Soc., 1950, 56c), probably differ in the location of the phosphoryl residue on the sugar. More recently, Cohn and Volkin (*Nature*, 1951, **167**, 483) have demonstrated in the products of enzymic degradation of calf liver ribonucleic acid the presence of 5'-phosphorylated nucleosides differing from the isomers previously found. All these results are in accordance with the formulation of a ribopolynucleotide as a series of nucleosides which are united by double esterification with phosphoric acid and, on hydrolysis to monophosphoric esters, yield isomeric products by fission of one or other of the ester linkages. This type of structure cannot be regarded as proved unless first it can be shown that doubly esterified ribose residues are present in the nucleic acid molecule. In the work now to be described, uncombined ribose hydroxyl groups have been labelled by methylation and the number of hydroxyl groups originally phosphorylated has been determined by examination of the carbohydrates obtained by hydrolysis of the methylated nucleic acid.

Methylation of Yeast Ribonucleic Acid.—Of the techniques available for methylating sugars, that due to Purdie and Irvine (*J.*, 1903, 1021) using methyl iodide and silver oxide seemed the most suitable for the present purpose, but Levene and Jacobs record (Levene and Bass, "The Nucleic Acids," Chem. Catalog Co., New York, 1931, p. 208) that this reagent decomposes nucleosides and nucleotides faster than it methylates them, owing to the insolubility of the materials in organic solvents. It has now been found, however, that yeast ribonucleic acid can be methylated by vigorous shaking at 25° with methyl alcohol, methyl iodide, and silver oxide (Anderson, Barker, and Farrar, *Nature*, 1949, **163**, 445). The product resembled the original nucleic acid and contained approximately two methoxyl groups per nucleotide residue, one of which is presumed to be attached to phosphorus since it is removed by hot aqueous sodium hydroxide. In order to determine whether this method of methylation could give a true indication of the state of combination of the carbohydrate residues in the nucleic acid it was necessary to decide whether the treatment was accompanied by any degradation which might result in methylation of hydroxyl groups originally phosphorylated; and, conversely, whether the technique employed achieved methylation of all the uncombined carbohydrate hydroxyl groups. Determination of the diffusion coefficients of the methylated nucleic acid and of the starting material indicated that the nucleic acid had not suffered appreciable reduction in molecular size during methylation. As far as the authors are aware, carbohydrates have not previously been methylated under such mild conditions and, in order to determine the efficiency of the method and also the behaviour of nitrogenous systems towards the reagents, the nucleosides guanosine, adenosine, and uridine have been subjected to the same treatment.

Methylation of Nucleosides.—After repeated methylation, guanosine and adenosine yielded hygroscopic glassy products of rather indefinite composition which approximated to pentamethyl derivatives. After hydrolysis, 2 : 3 : 5-trimethyl D-ribose, identical with synthetic material (Barker, *J.*, 1948, 2035), was obtained in each case and the two methylated nucleosides yielded respectively a dimethylguanine and a dimethyladenine. Derivatives of these purines had melting points 6—7° higher than those recorded for corresponding compounds obtained after methylation of guanosine and adenosine with methyl sulphate (Bredereck, Müller, and Berger, *Ber.*, 1940, **73**, 1058). No evidence was obtained on which to base structures for the methylated purines but it is considered probable that they are identical with those prepared by the German workers and that the two methylating agents behave similarly towards the nucleosides. In no case was a monomethylguanine or monomethyladenine obtained as described by Bredereck, Haas, and Martini (*Ber.*, 1948, **81**, 307).

Methylation of uridine gave crystalline 1-methyl-3-(2 : 3 : 5-trimethyl D-ribosyl)uracil which, after hydrogenation and hydrolysis, yielded 2 : 3 : 5-trimethyl ribose and 4 : 5-dihydro-1-methyluracil. In none of the above methylated nucleosides was any partly methylated ribose present in sufficient quantity to be observed during fractional distillation

of the hydrolysis product. However, since in subsequent experiments with the methylated nucleic acid it was envisaged that the more sensitive techniques of partition chromatography would be used, an estimate of the completeness of methylation was made by examining the carbohydrate residues from the crude methylated nucleosides by this method. This showed in each case intensely staining spots corresponding to 2 : 3 : 5-trimethyl ribose. Other spots of lower R_P value were observed, which are believed to correspond to partly methylated riboses, but these more slowly moving components gave such faint spots that it was concluded that methylation was virtually complete and that incompleteness of methylation to this small extent could in no way influence the interpretation of results obtained with the methylated nucleic acid.

Since neither methylated guanosine nor methylated uridine possesses a methoxyl group in the nitrogenous part of the molecule, it is reasonable to assume that, of the methoxyl groups present in the methylated nucleic acid, those which are not removed by alkaline hydrolysis are located on the ribose residues. Therefore, since the initial rapid methylation stopped abruptly when an average of approximately one methoxyl group per ribose residue had been introduced into the polynucleotide, it is concluded that, on the average, two carbohydrate hydroxyl groups per residue are esterified with phosphoric acid. This is also in agreement with the approximate equality of the percentage of ether-methoxyl and ester-methoxyl groups. As far as is known, this constitutes the first positive evidence of the existence of multiple esterification of carbohydrate residues in yeast ribonucleic acid.

Examination of the Carbohydrate Residues of Methylated Yeast Ribonucleic Acid.—In order to facilitate the liberation of the pyrimidine-bound ribose, the methylated nucleic acid was hydrogenated until the absorption of the solution between 260 and 270 mμ was constant at approximately half its original value. The resulting material was hydrolysed with N/10-sulphuric acid at 100° for two hours, by which time the reducing power of the solution had become constant. Examination of the resulting mixture of sugars on the paper chromatogram revealed three fractions having the same R_P values as ribose, 5-methyl ribose (Levene and Stiller, *J. Biol. Chem.*, 1934, **104**, 299), and 2 : 3-dimethyl ribose (Barker and Lock, *J.*, 1950, 23) respectively. There was also an intensely reducing spot on the starting line, which contained organically bound phosphoric acid. This was unexpected since it has been shown (Levene and Jorpes, *J. Biol. Chem.*, 1929, **81**, 575) that hydrogenation of the pyrimidine ring reduces the stability towards acid, not only of the glycosidic linkage, but also of the phosphoryl group of cytidylic acid. It was found, however, that whereas acid hydrolysis of yeast ribonucleic acid results in a rapid mineralisation of the phosphoric acid residues of the purine nucleotides, followed by a slow hydrolysis of the pyrimidine nucleotides, no such discontinuity in the hydrolysis of the methylated polynucleotide could be discerned. Furthermore, fission of the carbohydrate–phosphoric acid linkage took place at approximately the same rate as the hydrolysis of the ester-methoxyl groups since examination of the products on the paper chromatogram after varying periods of hydrolysis, indicated that phosphorus-containing reducing substances were present on the starting line so long as mineralisation of the phosphoric acid was incomplete. For this reason it was necessary to carry out a prolonged hydrolysis in order to achieve complete liberation of the carbohydrate. This introduced the further difficulty that the liberated sugars suffered considerable decomposition which resulted in " streaking " on the chromatogram. The conclusion was reached that under no conditions could full recovery of the carbohydrates be achieved. It was therefore decided to investigate the manner in which the proportions of the three fractions travelling down the chromatogram varied with time of hydrolysis.

In order to apply the method of Hirst, Hough, and Jones (*J.*, 1949, 928) to the determination of carbohydrates in eluates from the chromatograms, it was necessary to remove purine bases which reacted with the hypoiodite ion under the conditions used. The hydrolysates were neutralised and concentrated and the residues extracted with methyl alcohol. Chromatography on paper of the resultant solution indicated that interfering substances had been largely removed. The carbohydrate fractions were eluted from the chromatogram, transferred to a second chromatogram, and developed again either with the same or with a different solvent. Eluates from transverse strips of the paper were

titrated with hypoiodite. Except where the aniline hydrogen phthalate spraying reagent indicated carbohydrate material, reducing substances were present on the chromatogram in only small concentration.

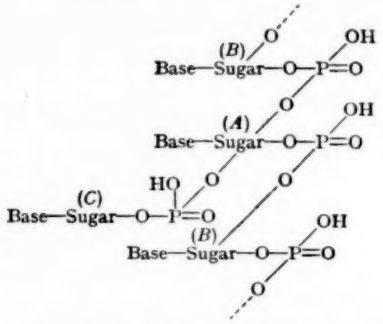
In the annexed table the proportions of what are believed, on the basis of their R_P values, to be ribose, monomethyl ribose and dimethyl ribose are seen to vary with the time of hydrolysis. Since it is not feasible to allow hydrolysis to proceed to completion, an absolute value for the ratios of the three fractions cannot be obtained. However, it is clear that, within the limits of the accuracy of the methods employed, the ratio of ribose

Time of hydrolysis (hours)	Molecular proportion of		
	ribose	monomethyl ribose	dimethyl ribose
3·5	0·95	0·6	1
60	1·1	1·35	1

to dimethyl ribose remains constant at about unity, whereas the proportion of monomethyl ribose increases with time of hydrolysis. Since test experiments indicated that demethylation during hydrolysis is negligible, it is reasonable to assume that the ratio of ribose to dimethyl ribose residues in the methylated polynucleotide is approximately unity, and that the molecular proportion of monomethyl ribose is something in excess of 1·4. After hydrolysis for 60 hours, approximately 70% of the phosphoric acid has been mineralised. Even if it is assumed, therefore, that further mineralisation would yield only monomethyl ribose, the proportion of this fraction would only rise to 2·8. Thus, although it is impossible to state with a high degree of certainty the proportions of the three carbohydrate fractions in the methylated polynucleotide, without attributing to the results greater accuracy than is warranted, it may be concluded that each fraction forms a major constituent of the mixture.

Discussion

From the results summarised above, it appears that triply, doubly, and singly phosphorylated ribose residues are present in the molecule of yeast ribonucleic acid. This conclusion involves three assumptions. First, that the unsubstituted ribose does not arise through failure to methylate all available hydroxyl groups; secondly, that the dimethyl ribose is not produced from simple nucleotides formed by degradation of the polynucleotide; thirdly, that the mixture of carbohydrates analysed is representative of the carbohydrate residues in the methylated polynucleotide. The first two assumptions have been discussed above and are considered to be justified. In every experiment, methylation resulted in the introduction of an average of one methoxyl group per ribose



residue. This means that the molecular ratio of ribose to dimethyl ribose should be unity, and this is found experimentally. Furthermore, the proportion of monomethyl ribose has been found to vary only with time of hydrolysis and to be otherwise reproducible. It is concluded, therefore, that incomplete recovery of carbohydrate incurred in working up the hydrolysate involves loss of each fraction to approximately the same extent. Thus the third assumption is also believed to be justified. On the basis of the results now presented, it is suggested that the ribonucleic acid of yeast consists of a branched chain

of nucleotides of the annexed type. In such an arrangement of nucleotides, ribose, monomethyl ribose, and dimethyl ribose would arise from residues marked (*A*), (*B*), and (*C*) respectively. On the basis of the quantitative results quoted above, branching is believed to occur on the average at every 2·4—3·8 nucleotides along a straight chain. Nothing can be said regarding the size of the branches or whether further ramification exists within them, since these factors would not affect the proportions of the carbohydrate fractions. Branching at phosphoric acid centres has previously been suggested by Fletcher, Gulland, and Jordan (*loc. cit.*), although doubts as to the validity of the conclusions have been expressed (Schmidt, *Ann. Rev. Biochem.*, 1950, **19**, 149). It must be emphasised, however, that branching at carbohydrate centres as is now postulated does not preclude the occurrence of branching also at phosphoric acid centres. On the contrary, no conclusion may be drawn from the present results concerning the numbers of primary and secondary phosphoric acid dissociations, in spite of what has been inferred by Schmidt (*loc. cit.*) and by Baddiley (*Ann. Reports*, 1950, **47**, 253) from preliminary publications of our results (Barker, Abstr. 1st Intern. Congr. Biochem., 1949, p. 216; Anderson, Barker, and Farrar, *loc. cit.*). Although no supporting evidence was produced, and no indication of its possible nature given, a branched structure has been suggested by Carter and Cohn (*J. Amer. Chem. Soc.*, 1950, **72**, 2604) to explain the preferential removal of pyrimidine nucleotides from yeast ribonucleic acid by ribonuclease. In the present studies it has not been possible to determine whether for instance the pyrimidine nucleotides are present largely in the side chains, owing to the stability of the ester groups of the methylated nucleic acid towards hydrolysis. However, it is proposed in the future to determine the degree of branching in various oligonucleotides.

The dimethyl ribose fraction, on prolonged chromatography, remains as a single spot, but the R_F value is found to be slightly different from that of 2 : 3-dimethyl ribose. Also, since periodate oxidation of the material on the paper (Buchanan, Dekker, and Long, *J.*, 1950, 3162) produces no formic acid, it is concluded that 2 : 5-dimethyl ribose alone is present. It is therefore tentatively suggested that the end nucleotides of branches are esterified at position 3′. If partition chromatography of the monomethyl ribose fraction is continued for a prolonged period, the spot exhibits a waist, the front part coinciding with the position of 5-methyl ribose. It appears, therefore, that the monomethyl ribose fraction contains at least two isomers, one of which may be 5-methyl ribose. In the unbranched parts of the molecule ester groups may therefore be present at any or all of the three possible positions. A comprehensive examination of the monomethyl and dimethyl ribose fractions is being undertaken but in any event, since at the sites of branching the ribose residues are triply esterified, the present results are in accordance with the isolation of isomeric nucleotides as reported by Cohn (*loc. cit.*). It is considered desirable now to record the results obtained so far, in view of the postulation of the new branched structure and the bearing which the results may have on researches in progress in other laboratories.

Experimental

Guanosine and adenosine were prepared by the method of Bredereck, Martini, and Richter (*Ber.*, 1941, **74**, 694), and uridine by that of Harris and Thomas (*J.*, 1948, 1936). Yeast ribonucleic acid (Pharmaco-Chemical Products Co.) was purified by the method of Sevag, Lackman, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425).

Methylation Technique.—The following procedure was found to yield products from nucleosides and nucleic acid, the methoxyl content of which was not appreciably altered by further treatments. The dried material (2·8 g.), suspended in methyl alcohol (dried by the method of Lund and Bjerrum, *Ber.*, 1931, **64**, 210) (15 c.c.), was vigorously shaken at 25° for 24 hours with silver oxide (2·5 g.) and methyl iodide (2·5 c.c.). Four further additions of silver oxide (2·5 g.) and methyl iodide (2·5 c.c.) were made at intervals of 12 hours and shaking was then continued for a further 12 hours. Silver salts were removed by filtration and extracted three times with hot methyl alcohol (60 c.c.). Solvent was removed below 35° from the combined filtrates, leaving a pale straw-coloured syrup.

Methylated Purine Nucleosides.—The syrupy methylated product was repeatedly rubbed with ether, and the solvent removed under reduced pressure leaving, as a hygroscopic brittle

glass, methylated guanosine (Found: C, 49·9; H, 6·5; N, 17·7; OMe, 24·5. Calc. for $C_{15}H_{23}O_5N_5$: C, 51·0; H, 6·5; N, 19·8; OMe, 26·4%), or methylated adenosine (Found: C, 49·5; H, 6·4; N, 19·3; OMe, 28·5. Calc. for $C_{14}H_{21}O_4N_5$: C, 53·4; H, 6·8; N, 20·8; OMe, 27·6%).

Methylated Uridine.—The crude methylated product had b. p. 132°/10^{-4} mm. and from the distillate 1-*methyl*-3-(2 : 3 : 5-*trimethyl* D-*ribosyl*)*uracil* separated in colourless needles which, after recrystallisation from light petroleum (b. p. 60—80°), had m. p. 96—98° (Found: C, 52·4; H, 6·6; N, 9·6; OMe, 31·9. $C_{13}H_{20}O_6N_2$ requires C, 52·0; H, 6·7; N, 9·3; OMe, 31·0%). In subsequent experiments the crude methylated product crystallised without previous distillation.

Methylated Nucleic Acid.—The crude methylated syrup was rubbed with acetone and the pale straw-coloured amorphous solid was collected by centrifugation, washed with ether, and dried in a vacuum-desiccator over phosphoric oxide [Found, in two preparations: C, 39·0, 39·2; H, 5·9, 6·0; N, 12·6, 12·2; OMe, 16·3, 16·4. Calc. for $C_{53}H_{77}O_{28}N_{15}P_4$ (a polymerised tetranucleotide containing 8OMe, and 7NMe groups per tetranucleotide): C, 42·5; H, 5·2; N, 14·1; OMe, 16·6%]. A portion of the product (5·4 mg.) was heated at 100° with N/10-sodium hydroxide (0·4 c.c.) for 4 hours. After neutralisation with N/10-hydrochloric acid, the solution was evaporated to dryness in a vacuum-desiccator over phosphoric oxide, and the methoxyl content of the whole of the residue was determined (Found: OMe, 7·2%).

Measurement of Diffusion Coefficients.—The diffusion coefficients of purified yeast ribonucleic acid and of the methylated nucleic acid were compared either by the method of Fletcher, Gulland, Jordan, and Dibben (*loc. cit.*) or with Gage's apparatus (*Trans. Faraday Soc.*, 1948, **44**, 253). In the latter case, the material under test (approx. 50 mg.) was dissolved in N-sodium sulphate (50 c.c.) and allowed to diffuse through two layers of Whatman No. 1 filter paper into N-sodium sulphate (400 c.c.) for 2½ hours at 37°. The percentage of diffusion was calculated from measurements of optical density of the diffusate and the original diffusing solution. The ratio of the diffusion coefficients of the nucleic acid before and after methylation was found to be 1·14; cf. 1·06 (Fletcher, Gulland, Jordan, and Dibben, *loc. cit.*), 1·01 (Gage, *loc. cit.*).

2 : 3 : 5-*Trimethyl Ribose.*—(a) *From methylated guanosine and methylated adenosine.* The methylated nucleoside (5 g.), dried at room temperature in a vacuum over phosphoric oxide, was dissolved in methyl alcohol (25 c.c.) containing 10% of hydrogen chloride and set aside at room temperature for 72 hours. The solution (A, see below) was then poured into 4% aqueous sodium hydroxide (100 c.c.) with stirring, the temperature being kept below 20°, and was repeatedly extracted with chloroform leaving an aqueous residue B (see below). After drying of the combined extracts ($MgSO_4$), the solvent was removed under reduced pressure. The residue was distilled under reduced pressure, yielding trimethyl methyl-D-ribofuranoside, b. p. 130—136° (bath-temp.)/15 mm., n_D^{25} 1·4354 (Found: OMe, 59·9. Calc. for $C_9H_{18}O_5$: OMe, 60·2%). The trimethyl methyl-D-ribofuranoside was hydrolysed as described by Barker (*J.*, 1948, 2035), yielding 2 : 3 : 5-trimethyl D-ribose, b. p. 93—100°/0·01 mm., n_D^{25} 1·4522 (Found: OMe, 47·5. Calc. for $C_8H_{16}O_5$: OMe, 48·5%). The anilide had m. p. 55·5° alone or mixed with synthetic material (Found: N, 5·1; OMe, 34·6. Calc. for $C_{14}H_{21}O_4N$: N, 5·2; OMe, 34·9%).

(b) *From methylated uridine.* 1-Methyl-3-(2 : 3 : 5-trimethyl D-ribosyl)uracil (20 mg.) in water (1·5 c.c.) was hydrogenated in presence of Adams's platinum oxide catalyst at room temperature and pressure until the uptake of hydrogen corresponded to the reduction of one double bond. The solution, after removal of the catalyst, was made 0·2N with respect to sulphuric acid and boiled under reflux for 1½ hours. Sulphate ions were removed from the cooled solution by addition of barium carbonate and filtration. The filtrate was concentrated under reduced pressure and a sample was developed on the paper chromatogram with *n*-butyl alcohol–1% aqueous ammonia (Partridge, *Biochem. J.*, 1948, **42**, 238). A single component was observed having R_F 0·73. Synthetic 2 : 3 : 5-trimethyl ribose had R_F 0·72 on the same chromatogram. The product also had the same R_F values as the synthetic material in the following solvent systems: *n*-butyl alcohol–ethyl alcohol–1% aqueous ammonia (Partridge *loc. cit.*); *n*-butyl alcohol–acetic acid–water (Partridge, *loc. cit.*); ethyl acetate–pyridine–water (Jermyn and Isherwood, *ibid.*, 1949, **44**, 402).

Chromatographic examination of hydrolysates of methylated guanosine, methylated adenosine, and hydrogenated crude methylated uridine was carried out similarly.

Isolation of Methylated Adenine.—Solution A (above) obtained from methylated adenosine was cooled to 0° and the dimethyladenine hydrochloride which was deposited was collected by filtration. It separated from aqueous ethyl alcohol (85%) in colourless needles, m. p.

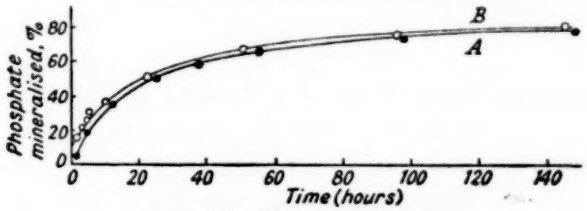
218—224° (decomp.) (Found : N, 35·3. Calc. for $C_7H_9N_5$,HCl : N, 35·1%). It was converted into the picrate, m. p. 242° (Found : N, 28·6. Calc. for $C_{13}H_{12}O_7N_8$: N, 28·6%).

Isolation of Methylated Guanine.—Solution B (above), obtained from methylated guanosine, was neutralised with acetic acid and then made alkaline with ammonia solution. The precipitated methylated guanine was collected by filtration and suspended in aqueous ethyl alcohol (85%), and hydrogen chloride was passed through the solution at 0° until crystallisation had taken place. The dimethylguanine hydrochloride was collected by filtration; it separated from ethyl alcohol in colourless needles, m. p. 282° (Found : C, 38·5; H, 5·5; N, 32·1. Calc. for $C_7H_9ON_5$,HCl : C, 39·0; H, 4·6; N, 32·5%).

4 : 5-*Dihydro*-1-*methyluracil.*—1-Methyl-3-(2 : 3 : 5-trimethyl D-ribosyl)uracil (0·55 g.) was hydrogenated and hydrolysed by sulphuric acid as described above, and, after removal of sulphate ions by barium carbonate and filtration, the solution was concentrated under reduced pressure to a small volume and percolated through a column of powdered cellulose. Elution of the column with light petroleum (b. p. 100—120°)–*n*-butyl alcohol (7 : 3) gave a fraction which after removal of the solvent yielded **4** : 5-dihydro-1-methyluracil which separated from ethyl alcohol in needles, m. p. 129° (cf. Hotchkiss and Johnson, *J. Amer. Chem. Soc.*, 1936, **58**, 525) (Found : C, 46·5; H, 6·5; N, 21·6. Calc. for $C_5H_8O_2N_2$: C, 46·9; H, 6·3; N, 21·9%).

Hydrolysis of Methylated Nucleic Acid.—The rate of hydrolysis of methylated nucleic acid by acids was determined under various conditions. A solution of the material (approx. 1 mg.

Hydolysis of methylated yeast ribonucleic acid.



A, in N/100-HCl; *B*, in N/10-HCl.

per c.c.) was added to an appropriate volume of either hydrochloric or sulphuric acid and heated in a boiling-water bath. At intervals aliquots were withdrawn and free phosphoric acid was determined by Fiske and Subbarow's method (*J. Biol. Chem.*, 1925, **66**, 375). With concentrations of acid between N/100 and N/5 and with both hydrochloric and sulphuric acids, hydrolysis proceeded at closely similar rates. Representative results are illustrated in the figure. A neutral solution of the methylated nucleic acid, hydrogenated and hydrolysed as described below, was examined by partition chromatography. The R_F values of the hydrolysis products are recorded in the annexed table.

Solvent system	R_F A	B	C	Solvent system	R_F A	B	C
Ribose	0·17	0·15	0·52	Hydrolysis products (i)	0·16	0·16	0·52
5-Methyl ribose	0·34	0·33	0·62	,, ,, (ii)	0·34	0·32	0·64
2 : 3-Dimethyl ribose ...	0·58	0·60	0·72	,, ,, (iii)	0·57	0·60	0·78

A, *n*-Butanol–water; [1] B, *n*-butanol–water–1% aqueous ammonia; [1] C, ethyl acetate–pyridine–water.[2]

[1] Partridge, *Biochem. J.*, 1948, **42**, 238; [2] Jermyn and Isherwood, *loc. cit.*

Methylated yeast ribonucleic acid (100 mg.) was dissolved in water (30 c.c.) and hydrogenated at room temperature and pressure in presence of Adams's platinum oxide catalyst added portionwise (5 times 50 mg.) at intervals during 5 days. After the final addition of catalyst further hydrogenation produced no change in the absorption of the solution in the region of 260 mμ. After removal of the catalyst by filtration, the solution was made 0·5N with respect to sulphuric acid and was heated in a boiling water-bath. After varying periods of time the solution was cooled, neutralised with N-sodium hydroxide, and concentrated to dryness under reduced pressure. The residue was repeatedly extracted with boiling methyl alcohol (50 c.c.), and the combined extracts were concentrated under reduced pressure to small bulk and transferred to the paper chromatogram in a series of spots along the starting line. After development with ethyl acetate–pyridine–water (Jermyn and Isherwood, *loc. cit.*) and drying, one lane of the paper was removed and sprayed with aniline hydrogen phthalate (Partridge, *Nature*,

1949, **164**, 443), revealing the positions of the three sugar zones. Transverse strips carrying the three sugar fractions were cut from the remainder of the paper and were separately eluted with water (5 c.c.) applied dropwise to the paper from a burette. Test experiments indicated that this procedure removed all carbohydrates from the paper. Each eluate was then concentrated to small bulk and transferred to a second chromatogram, which was irrigated with the same mixture of solvents. The carbohydrate fraction on each of the three resultant chromatograms was estimated as previously described, by dividing the chromatogram into transverse strips, eluting the strips with water (5 c.c.), and subjecting the eluates to the hypoiodite titration procedure of Hirst, Hough and Jones (*loc. cit.*). The results were:

Time of hydrolysis, hours	Carbohydrate on chromatogram expressed as c.c. of N/100-sodium thiosulphate		
	Ribose	Monomethyl ribose	Dimethyl ribose
3·5	0·800	0·515	0·845
60	1·330	1·630	1·205

The presence of combined phosphoric acid in the eluates from chromatograms was detected by Fiske and Subbarow's method (*loc. cit.*). The presence of purines in the eluates from chromatograms was detected by means of the Beckman DU spectrometer.

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74. *Titanium Tetrachloride as a Catalyst in the Friedel–Crafts Reaction. Part I. Acylation.*

By N. M. CULLINANE, S. J. CHARD, and D. M. LEYSHON.

The acylation of benzene, toluene, and anisole in contact with titanium tetrachloride as a catalyst has been studied, the ease of reaction being in the above order. Acids and acid chlorides and anhydrides were the acylating agents, acids being the least and acid anhydrides the most effective. From acid chlorides the yields of ketones increased in the order acetyl, *n*-propionyl, *n*-butyryl, benzoyl. In general, other conditions being constant, there was an optimum temperature and reaction time.

The most satisfactory yields were obtained when 2—3 equivalents of titanium tetrachloride were used. Moreover, in the acylation of toluene and anisole almost exclusive *para*-substitution occurred.

o-Benzoylbenzoic acid was not formed from phthalic anhydride and benzene, and with toluene the chief product was 3 : 3-di-*p*-tolylphthalide.

TITANIUM TETRACHLORIDE has been used only to a minor extent in reactions of the Friedel–Crafts type. Stadnikov and Kashtanov (*Ber.*, 1928, **61**, 1389) state that no benzophenone is formed from benzene and benzoyl chloride in the presence of this catalyst, and Galle (*J. Gen. Chem. Russia*, 1938, **8**, 402) claims that, though naphthalene is likewise unaffected, methoxynaphthalenes do react. Dermer *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2881; 1942, **64**, 464) have compared the effect of several catalysts, including titanium tetrachloride, on the reaction between toluene and acetyl chloride.

In the present work, the acylation in contact with titanium tetrachloride of benzene, toluene, and anisole was studied; the yields of ketone increased in that order. In general the Perrier sequence (*Ber.*, 1900, **33**, 815) was followed, *i.e.*, the catalyst was first added to the acylating agent, forming a complex, the compound to be acylated being subsequently introduced. Although titanium tetrachloride was found to be less efficient than aluminium chloride, comparable yields of ketones were obtained in most cases. Both acetylation and benzoylation were investigated, and acid chlorides, anhydrides, and acids were used as acylating agents. Anhydrides, which gave the highest, and acids, which gave the lowest, yields, do not appear to have been previously used for acylations in conjunction with this catalyst. Also, the yields obtained in benzoylation were higher than in acetylation.

As well as acetyl chloride, *n*-propionyl and *n*-butyryl chlorides were used, increased yields of ketones being obtained as the series was ascended. The most satisfactory results were obtained when at least one equivalent of catalyst was employed; this was presumably due, as in the case of aluminium chloride, to the formation of an inactive complex with

FIG. 1. *Variation of yield with time at constant temp. in reactions with toluene (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*

1, Acetyl chloride at 0° (3). 2, *n*-Propionyl chloride at 0° (3). 3, *n*-Butyryl chloride at 0° (3). 4, Benzoyl chloride at 35° (1). 5, Acetic anhydride at 0° (2·2).

FIG. 2. *Variation of yield with time at constant temp. in reactions with anisole (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*

1, Acetyl chloride at 40° (2). 2, *n*-Butyryl chloride at 25° (2). 3, Benzoic anhydride at 40° (2·2). 4, Acetic acid at 80° (3).

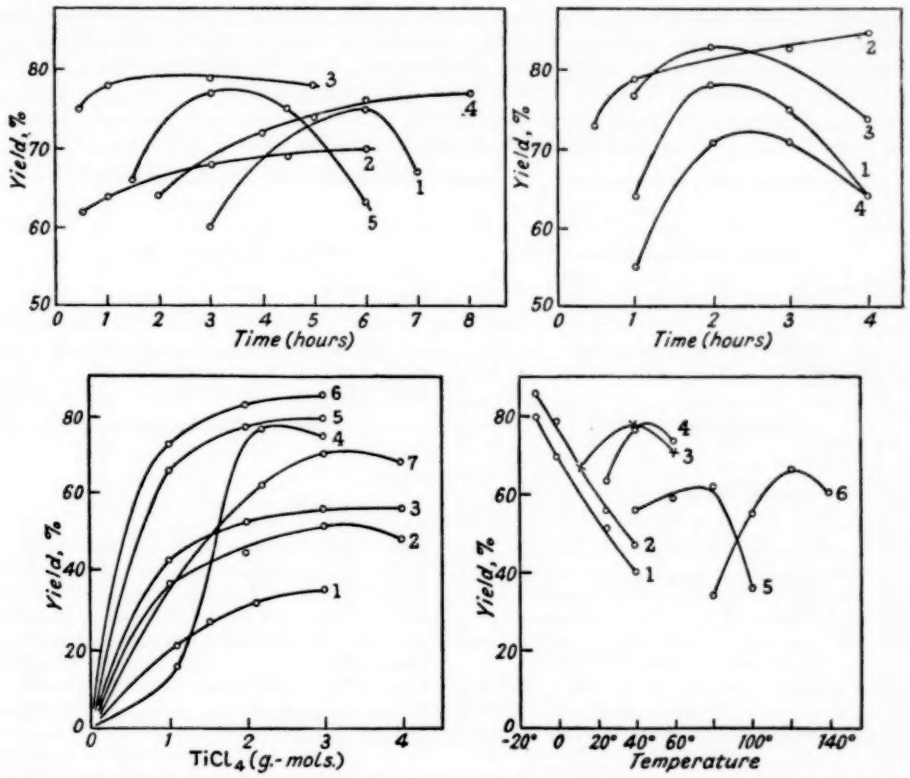

FIG. 3. *Effect on yield of variation in the proportion of catalyst at constant time and temperature.*

1, Acetyl chloride and toluene, 20 min. at 20—25° (Dermer *et al.*, *loc. cit.*). 2, *n*-Propionyl chloride and toluene, 3 hours at 25°. 3, *n*-Butyryl chloride and toluene, 3 hours at 25°. 4, Acetic anhydride and toluene, 3 hours at 0°. 5, *n*-Propionyl chloride and anisole, 3 hours at 40°. 6, *n*-Butyryl chloride and anisole, 3 hours at 25°. 7, Acetic acid and anisole, 3 hours at 80°.

FIG. 4. *Effect on yield of variation in temperature with constant proportion of catalyst (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*

1, *n*-Propionyl chloride and toluene, 3 hours (3). 2, *n*-Butyryl chloride and toluene, 3 hours (3). 3, Acetyl chloride and anisole, 2 hours (2). 4, *n*-Propionyl chloride and anisole, 3 hours (2). 5, Acetic acid and anisole, 3 hours (2·2). 6, Benzoic acid and anisole, 3 hours (3).

the ketone of the type $CORR',TiCl_4$. In practice about 3 equivalents of catalyst were the most successful.

The anhydrides not only gave good yields, but also cleaner products with less formation of tars. Here at least 2 g.-mols. of catalyst per g.-mol. of anhydride were needed to give the best results; poor yields previously obtained with aluminium chloride have been

ascribed by Noller and Adams (*J. Amer. chem. Soc.*, 1924, **46**, 1889) to the use of insufficient catalyst.

When acids were used for acylation about 3 equivalents were found to be the most satisfactory and although the yields obtained with benzene were small, a considerable improvement was noted with toluene and especially with anisole.

Fig. 3 gives a selection of reactions showing the effect on the yield of increasing the proportion of titanium tetrachloride, other conditions being constant. In general, the best results were obtained with 2—3 equivalents of titanium tetrachloride, and in many cases reduced yields were observed when more catalyst was used.

In reactions with anhydrides intermediate formation of acid chlorides took place. It was also found with toluene (Fig. 1) and anisole (Fig. 2) that, other conditions being constant, there was an optimum reaction period below or above which yields tended to diminish or at least not to increase. Furthermore, Fig. 4 indicates that in certain experiments increase of temperature resulted in diminution in yield.

Acylations with 0·1 *g.-mol. of acylating agent.*

(Quantities are given in terms of g.-mols., except those marked †, which are in terms of c.c.)

$TiCl_4$	C *	Temp.	Time (hours)	Yield, %	Note
		Benzene and acetyl chloride.			
0·15	0·2	0°	24	7·5	1
0·3	0·2	0	24	4	2
		Benzene and acetic anhydride.			
0·22	40 †	0	24	35	3
		Toluene and acetyl chloride.			
0·3	25 †	25	3	66	6
		Toluene and acetic acid.			7
0·3	25 †	100	1	15	8
0·22	50 †	100	3	10	
		Anisole and acetyl chloride.			13
0·1	0·15	40	2	65	—
		Anisole and n-*propionyl chloride.*			
0·2	0·2	40	1	79	14
		Anisole and n-*butyryl chloride.*			
0·2	0·2	60	3	89	15
		Anisole and acetic anhydride.			13
0·22	0·15	40	2	71	16
0·22	0·15	40	4	76	17
0·3	0·15	40	2	69	

$TiCl_4$	C *	Temp.	Time (hours)	Yield, %	Note
		Benzene and benzoyl chloride.			
0·2	25 †	‡	11	32	4
0·2	25 †	50°	7	6	—
0·2	25 †	15	65	3	—
		Benzene and benzoic anhydride.			
0·22	40 †	‡	10	65	5
0·22	40 †	10	90	3	—
		Toluene and benzoyl chloride.			
0·12—0·2	25 †	17	24	81	—
		Toluene and benzoic anhydride.			
0·22	40 †	115	4	95	9
0·22	50 †	100	6	85	—
0·22	50 †	80	8	74	10
0·22	50 †	13	63	60	—
0·22	50 †	17	24	22	—
		Toluene and benzoic acid.			
0·3	50 †	‡	2	49	11
0·3	50 †	110	5	30	12
		Anisole and benzoyl chloride.			13
0·15	0·15	40	1	91	18
		Anisole and benzoic anhydride.			19
0·22	0·15	‡	1	97	—
		Anisole and benzoic acid.			20
0·4	0·2	120	1·5	63	
0·3	0·2	120	1·5	66	21

* C = compound acylated. ‡ = Reaction mixture heated under reflux.

Notes. With other conditions throughout as stated, further yields obtained were as follows: (1) After 13 hours 7%, 6 hours 6%. (2) At 25° 3%. (3) The same yield was obtained when the acetic anhydride was added to a mixture of titanium tetrachloride and benzene or by the Perrier sequence. (4) After 5 hours 16%, 8·5 or 15 hours 30%. (5) After 6·5 hours 54%. (6) Cf. Dermer *et al.* (*loc. cit.*). (7) Titanium tetrachloride was added to a mixture of toluene and acid. (8) After 3 hours 8%. (9) With 0·3 g.-mol. of titanium tetrachloride 90%. (10) At 60° 66%. (11) After 5 hours 31%. (12) At 100° 2%. (13) CS_2 (40 c.c.) also present. (14) After 0·5 hour 70%, 2 or 3 hours 77%. (15) At 25° 83%, 40° 85%. (16) Perrier sequence; when titanium tetrachloride was added to anisole and acetic anhydride, yield 80%. (17) After 0·5 hour 58%, 1 hour 64%, 3 hours 73%. (18) After 2 or 4 hours 85%. (19) CS_2 (60 c.c.) also present. (20) Titanium tetrachloride was added to a mixture of anisole and benzoic acid. (21) At 140° 60%.

In all reactions with toluene and anisole almost exclusive *para*-substitution occurred.

Following Illari's views (*Gazzetta*, 1948, **78**, 687; cf. Groggins and Detwiler, *Ind. Eng. Chem.*, 1950, **42**, 1690) on the mechanism of the Friedel–Crafts synthesis with anhydrides and acids in the presence of aluminium chloride, the equations for the reactions with titanium tetrachloride may be indicated as follows:

$$(R{\cdot}CO)_2O + 3TiCl_4 = TiOCl_2 + 2R{\cdot}OCl,TiCl_4$$
$$R{\cdot}CO_2H + TiCl_4 = R{\cdot}CO{\cdot}O{\cdot}TiCl_3 + HCl$$
$$R{\cdot}CO{\cdot}O{\cdot}TiCl_3 + TiCl_4 = TiOCl_2 + R{\cdot}COCl,TiCl_4$$

In accordance with this view, 3 g.-mols. of catalyst are needed for the best yields with anhydrides, and 2 with acids. It should also be noted that, although intermediate formation of acid chlorides occurs when the anhydrides are used, yet with acids only negligible amounts of such products are obtained.

An unusual result was obtained when phthalic anhydride reacted with toluene in contact with titanium tetrachloride. No 2-*p*-toluoylbenzoic acid was formed, but 3 : 3-di-*p*-tolylphthalide was produced in good yield:

This compound was previously obtained from phthaloyl chloride (Limpricht, *Annalen*, 1898, **299**, 286; de Berchem, *Bull. Soc. chim.*, 1884, **42**, 168) or phthalic anhydride (Limpricht, *Annalen*, 1898, **299**, 300; von Pechmann, *Ber.*, 1881, **14**, 1865; Friedel and Crafts, *Ann. Chim. Phys.*, 1888, **14**, 447) and toluene in the presence of aluminium chloride, notably when the quantity of catalyst used was less than 1 equivalent.

Experimental

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Numerous experiments were carried out under different conditions, the proportions and order of addition of the reactants and catalyst being varied as well as duration and temperature. All materials were dried and redistilled before use, and all essential precautions taken to exclude moisture. The yields stated, which are based in all cases on the acylating agent, are only approximate, though repetition of the experiments in many cases gave comparable results; these are summarised in the table and figures.

Though the yields given are based on the formation of 1 mole of ketone from 1 of anhydride, it should be pointed out that Groggins and Nagel (*Ind. Eng. Chem.*, 1934, **26**, 1313) claim that at least part of the second acyl group in an acid anhydride is available for reaction when a large excess of catalyst is employed.

Perrier's sequence was usually followed; stirring and cooling were applied during the mixing process, and agitation was continued throughout each experiment. Water or dilute hydrochloric acid was then added, and the organic layer separated, washed successively with dilute hydrochloric acid and water, and dried ($CaCl_2$). In general, the ketones were obtained by fractional distillation at the ordinary or reduced pressure and, when solid, were purified by recrystallization and the weight of product was ascertained. Liquid ketones were estimated (as well as identified) by conversion into the 2 : 4-dinitrophenylhydrazone, this process having been found by test to give accurate results: 2 : 4-Dinitrophenylhydrazine (2 g.) was dissolved by warming in concentrated sulphuric acid (4 c.c.), followed by ethyl alcohol (20 c.c.). The product was kept for some time and then filtered. Sufficient of the reagent was added to the ketone (*ca.* 0·5 g.) dissolved in alcohol (20 c.c.), and heat was applied, whereupon precipitation occurred. The product was filtered off when cold and recrystallized from ethyl acetate or ethyl acetate–alcohol.

Acylation of Benzene.—With acetyl chloride, the best yields of acetophenone were obtained at 0°. The product was determined by conversion into the 2 : 4-dinitrophenylhydrazone, orange prisms, m. p. 237° (cf. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955). Acetic anhydride

gave better yields, and here also low temperatures were most successful. Acetic acid gave only a negligible yield.

The best yields of benzophenone from benzoyl chloride or benzoic anhydride and benzene were achieved by refluxing the reactants. The anhydride was here also the superior acylating agent, and the acid failed to afford any ketone.

Acylation of Toluene.—Satisfactory yields were obtained with acetyl chloride and acetic anhydride, especially at low temperatures, but the acid gave only a small yield. The product in all cases consisted almost entirely of methyl *p*-tolyl ketone, b. p. 224°, m. p. 28°; 2 : 4-dinitrophenylhydrazone, red prisms, m. p. 257°. Roberts and Green (*J. Amer. Chem. Soc.*, 1946, **68**, 214) give m. p. 257—258°; Allen and Richmond (*J. Org. Chem.*, 1937, **2**, 222) give 248°.

Slightly improved yields were given with *n*-propionyl and still higher with *n*-butyryl chloride, low temperatures being again most effective. The products consisted almost entirely of the *para*-substituted derivatives. Ethyl *p*-tolyl ketone had b. p. 233° and gave a 2 : 4-*dinitrophenylhydrazone*, bright red needles, m. p. 201° (Found : N, 17·0. $C_{16}H_{16}O_4N_4$ requires N, 17·1%), and semicarbazone, m. p. 187° (cf. Baddeley, *J.*, 1944, 232). Propyl *p*-tolyl ketone had b. p. 250° and gave a 2 : 4-*dinitrophenylhydrazone*, orange-red plates, m. p. 191° (Found : N, 16·5. $C_{17}H_{18}O_4N_4$ requires N, 16·4%) and semicarbazone, m. p. 210° (cf. Tsukervanik and Terentieva, *J. Gen. Chem. Russia*, 1940, **10**, 1405).

Benzoic anhydride gave better yields than benzoyl chloride, and even the acid gave a moderately good yield. The product was almost entirely phenyl *p*-tolyl ketone, b. p. 328°, m. p. 58° [2 : 4-dinitrophenylhydrazone, orange crystals, m. p. 200° (cf. Grieve and Hey, *J.*, 1934, 1797)].

Acylation of Anisole.—Yields were consistently good, *para*-substituted ketones being almost exclusively formed. Use of carbon disulphide as solvent rendered the reaction mass easier to handle. The effectiveness of the acylating agents increased in the order acetyl < *n*-propionyl < *n*-butyryl < benzoyl chloride and moderate temperatures were most satisfactory except with acids, where higher temperatures gave the best yields.

p-Methoxyacetophenone had b. p. 258°, m. p. 38° [2 : 4-dinitrophenylhydrazone, scarlet prisms, m. p. 232° (cf. Borsche and Barthenheier, *Annalen*, 1942, **553**, 250)]. *p*-Methoxypropiophenone had b. p. 148°/15 mm., m. p. 27° [2 : 4-*dinitrophenylhydrazone*, red plates, m. p. 195° (Found : N, 16·2. $C_{16}H_{16}O_5N_4$ requires N, 16·3%). *p*-Methoxybutyrophenone had b. p. 160°/20 mm., m. p. 21° [2 : 4-*dinitrophenylhydrazone*, red prisms, m. p. 169° (Found : N, 15·5. $C_{17}H_{18}O_5N_4$ requires N, 15·6%)]. Phenyl *p*-tolyl ketone had m. p. 58°. *p*-Methoxybenzophenone had m. p. 62° [2 : 4-dinitrophenylhydrazone, orange prisms, m. p. 180° (cf. Chrodroff and Klein, *J. Amer. Chem. Soc.*, 1948, **70**, 1647)].

Action of Phthalic Anhydride on Toluene in the Presence of Titanium Tetrachloride.—A 60% yield of 3 : 3-di-*p*-tolylphthalide was obtained when toluene (40 c.c.) followed by titanium tetrachloride (57 g., 0·3 g.-mol.) was added to the anhydride (15 g., 0·1 g.-mol.). Hydrogen chloride was rapidly evolved as the mixture was heated to 100°. After 8 hours the contents were decomposed with dilute hydrochloric acid, excess of toluene was removed by distillation in steam, and the product cooled in ice and filtered off. The brown sticky solid was treated with excess of sodium carbonate solution, from which on acidification a little phthalic acid was obtained. The residue was washed with water and dried, the tarry portion being removed by grinding it with small amounts of ether, whereupon a white crystalline solid resulted. Recrystallisation from alcohol afforded white prisms, m. p. 117° (cf. Limpricht, *loc. cit.*).

We thank Messrs. Peter Spence and Sons, Ltd., for gifts of titanium tetrachloride and the Department of Scientific and Industrial Research for a Maintenance Grant to one of us (D. M. L.).

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75. *The Kinetics of the Thermal Decomposition of Olefins. Part II.**

By (Miss) M. J. Molera and F. J. Stubbs.

A comparative study has been made of the thermal decomposition of the following olefins in a static system : but-1-ene, pent-1-ene, hex-1-ene, hept-1-ene, but-2-ene, *iso*butene, 2-methylbut-1-ene, 3-methylbut-1-ene. Analyses of the products of the reaction for some of them were made by taking samples at different times. The observed pressure increase was shown to be a measure of the olefin decomposed, for at least the first part of the decomposition. The decomposition is in each case a first-order reaction, and the activation energies have been determined. *iso*Butene has been studied in more detail and a reaction mechanism is proposed. A brief study of the pyrolysis of ethylene has shown that over the range 600—800° polymerization and decomposition occur together, the latter predominating at higher temperatures.

Part I of this series (Ingold and Stubbs, *loc. cit.**) has dealt with the thermal decomposition of propylene in a static system. The decomposition was found to be a homogeneous first-order reaction with activation energy 57·1 kcal./g.-mol. The present paper extends the investigation to the olefins named in the summary.

Several investigations of the pyrolysis of higher olefins have been carried out but mostly in flow systems or under conditions of temperature and pressure different from those used in the static apparatus in the present work. Many of these investigations refer to the three butenes (Hurd and Spence, *J. Amer. Chem. Soc.*, 1929, **51**, 3566; Hurd, *J. Ind. Eng. Chem.*, 1934, **26**, 50; Tropsch, Parrish, and Egloff, *Ind. Eng. Chem.*, 1936, **28**, 581; Hurd and Blunk, *J. Amer. Chem. Soc.*, 1937, **59**, 1869; Steacie and Shane, *Canadian J. Res.*, 1938, **16**, *B*, 210; Rice and Haynes, *J. Amer. Chem. Soc.*, 1948, **70**, 964; Rice and Wall, *ibid.*, 1950, **72**, 3967), and to the pentenes (Gorin, Oblad, and Schmuck, *Ind. Eng. Chem.*, 1946, **38**, 1187; Hepp and Frey, *ibid.*, 1948, **41**, 827).

A comparative study of the series of olefins is interesting in that it provides information about the way in which the decomposition rate varies in the series of straight-chain Δ^1-olefins or in a group of isomeric olefins, knowledge of the products formed and their proportions giving an indication of the reaction mechanism. Moreover, since the thermal decomposition of a paraffin gives a lower paraffin and an olefin, for a complete interpretation of the paraffin results it is important to know the relative stability of various olefins. It is also of interest to compare behaviour in the paraffin and the olefin series.

Experimental

The apparatus and technique have already been described (Stubbs and Hinshelwood, *Proc. Roy. Soc.*, 1950, *A*, **200**, 458). The following olefins were standard samples from the National Bureau of Standards (U.S.A.) : Pent-1-ene, hex-1-ene, 2-methylbut-1-ene, 3-methylbut-1-ene. Hept-1-ene was a specially pure sample supplied by Imperial Chemical Industries Limited, Billingham.

The three butenes were prepared as follows : But-1-ene was prepared by the action of alcoholic potash on *n*-butyl iodide. The but-1-ene formed was condensed in a trap cooled with liquid air, then fractionated, the middle fraction only being collected. Its purity was tested by infra-red spectroscopy by Dr. R. L. Williams and Dr. H. W. Thompson and found to be 98 $\pm$ 2%. But-2-ene, prepared by dehydration of *sec.*-butyl alcohol with phosphoric oxide, was fractionated, and its purity, tested by infra-red spectrometry and mass spectrometry, was at least 95%. *iso*Butene was made by the dehydration of *tert.*-butyl alcohol with anhydrous oxalic acid at 80° and fractionated. Its purity was tested in the mass spectrometer.

Analyses of the gaseous reaction products were made in one of the two ways :

(1) By conventional methods in a Bone and Wheeler apparatus. Propylene and higher olefins were absorbed in 82·4% sulphuric acid (Hurd and Spence, *J. Amer. Chem. Soc.*, 1929, **51**, 3353), and ethylene in a saturated solution of mercuric acetate. Saturated hydrocarbons

* Part I, *J.*, 1951, 1749.

were determined by explosion with oxygen. Carbon dioxide was used as reference gas, a known amount being introduced into the reaction vessel together with the olefin. In this way, the absolute amount of product formed could be calculated. In the case of olefins that are liquid at room temperatures, the gaseous product and unchanged olefin were passed through a trap cooled with solid carbon dioxide to condense out the olefin at the moment of taking the sample, before introducing it into the Bone and Wheeler apparatus.

(2) By mass-spectrograph analysis. This work was carried out by Dr. C. J. Danby and Mr. I. A. Henderson. Helium was used as reference gas in this case. Difficulties were encountered, in particular the formation of higher polymers which interfered with the accurate estimation of lower olefins. The technique will be reported in detail elsewhere.

General Form of Δp*–Time Curves.*—With most of the higher olefins the initial portion of the Δp–time curve (where Δp is the observed increase of pressure in mm. of mercury) is a straight line passing through the origin, and there is the normal decrease in rate as the reaction comes to an end. Estimation of the initial rate presents no difficulty.

With *iso*butene and but-2-ene, and in some of the experiments on 2-methylbut-1-ene, and 3-methylbut-1-ene, there is at first a short time during which Δp is inappreciable and after which the slope of the curve rises quickly to a maximum, subsequently decreasing as the reaction comes to an end. This type of Δp–time curve is also observed with propylene. For comparative purposes the rate is taken as the maximum slope of the curve.

It now remains to consider how far the Δp–time curves give a definite measure of the rate at which olefin is used.

It was found for propylene over a range of different temperatures and pressures (Ingold and Stubbs, *loc. cit.*) that, for at least the first half of the reaction, the amount of propylene used is, after a short initial period, proportional to Δp.

It will now be shown that for *iso*butene Δp is in fact also a definite measure of the olefin consumed, *i.e.*, the plot of *iso*butene used against Δp is a straight line. It will also be shown that plots of the products formed (CH_4, C_2H_4, H_2, etc.) against Δp all yield straight lines. These do not pass exactly through the origin, some olefin initially being used without pressure change, but after quite a short interval, the rate of change of Δp becomes a reasonable measure of the rate of consumption of the olefin itself.

For the olefins above C_4 the amount of olefin used cannot be determined, but the plots of products formed against Δp all lie on straight lines. It is inferred therefore that for the higher olefins also the olefin consumed plotted against Δp would also yield a straight line, *i.e.*, that Δp is a reasonable measure of the reaction rate.

Order of the Reaction.—The variation of rate (from Δp–time curves) with initial olefin pressure is recorded for various temperatures in Table 1, and the results for some typical olefins are plotted in Fig. 1. In all cases the reactions are of the first order down to quite low pressures, where the characteristic transition towards the second-order occurs, in accordance with what might be expected from the process of collisional activation.

TABLE 1. *Variation of rate with pressure.**

But-1-ene, 540°	p_0	53	98·5	196·5	297·8	398	503·5			
	rate	1·2	2·1	4·8	7·7	11	13·8			
But-2-ene, 540°	p_0	93·5	117·5	198·5	305	364	449	518·5		
	rate	1·3	1·35	2·8	5·7	6·2	8·0	10·0		
*iso*Butene, 580°	p_0	52·5	116	206	298	361	421	483	514·5	
	rate	1·1	2·9	6·3	9·6	12·0	14·0	17·0	18·5	
Pent-1-ene, 480°	p_0	102·5	209·5	306·5	420·8	504				
	rate	2·5	5·7	8·2	10·8	13·6				
2-Methylbut-1-ene, 530°	p_0	100	163·5	216·5	300	354	435	496		
	rate	3·3	4·6	6·6	11·0	13·3	17·0	18·5		
3-Methylbut-1-ene, 520°	p_0	67	101	154	200·5	269	308·5	366·5		
	rate	2·9	3·5	6·5	8·8	12·8	15·5	19·0		
Hex-1-ene, 470°	p_0	36·5	99	149	202·5	252	301	353	412	
	rate	0·75	2·8	4·5	6·2	8·0	9·5	11·5	13·0	
Hept-1-ene, 470°	p_0	23·5	66	102·5	150	201·5	248	299·5	360	446
	rate	0·85	2·8	4·7	8·3	11·5	16·5	20·0	21·5	28

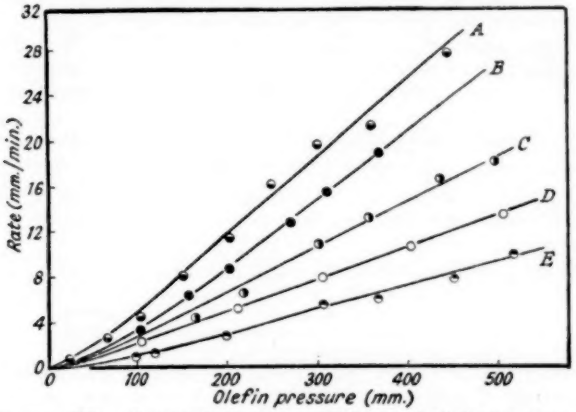
* All pressures (p_0) measured in terms of mm. of Hg. All rates are recorded as mm. of Hg/min.

It is of interest to see whether the Δp–time curves follow a first-order equation or whether the first-order behaviour is only shown by the initial rates.

For most of the olefins the actual relation between Δp and olefin consumed is not known. In the first-order equation $\ln a/(a - x) = kt$ the simplest assumption would be $x = \Delta p$ but,

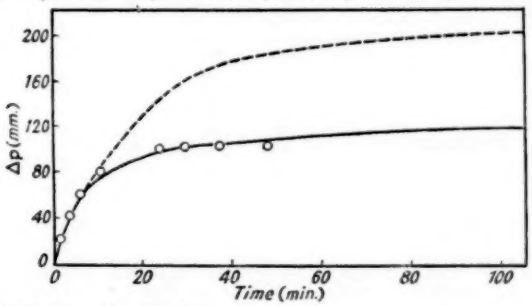
as Table 2 shows, for several olefins Δp_∞ is less than the initial pressure. If, however, we suppose $x = m\Delta p$, the values of m can be determined from the experimental curve and are recorded in the last column of Table 2. Fig. 2 shows for a typical case how with these values of m a theoretical first-order curve and an experimental curve agree over a considerable proportion of the reaction.

FIG. 1. *Rate–pressure curves for various olefins.*



A, *Hept*-1-*ene*, 470°. *B*, 3-*Methylbut*-1-*ene*, 520°. *C*, 2-*Methylbut*-1-*ene*, 530°. *D*, *Pent*-1-*ene*, 450°. *E*, *But*-2-*ene*, 540°.

FIG. 2. Δp–*time curve for the decomposition of* 200 *mm. of but*-1-*ene at* 560°.



Full curve : observed Δp.
○, *Theoretical points for first-order reaction ;* x = 2Δp.
Broken curve : Theoretical curve for first-order reaction ; x = Δp.

It has not been possible to fit results for hept-1-ene to such a curve, probably because of the secondary decomposition of the products; nor can the Δp–time curves for but-2-ene and *iso*butene be adjusted to a first-order equation because these curves show a sigmoid form.

TABLE 2. *Values of* $\Delta p_\infty / p_0$ *for different olefins.*

	$\Delta p_\infty / p_0$	Temp.	m		$\Delta p_\infty / p_0$	Temp.	m
Hept-1-ene	1·38	510°	—	But-2-ene	0·57	540	—
Hex-1-ene	0·97	500	1·2	2-Methylbut-1-ene	0·77	530	1
Pent-1-ene	0·80	500	1·6	3-Methylbut-1-ene	0·80	520	1·5
But-1-ene	0·62	560	2				

Activation Energy.—The activation energies for all the olefins are recorded in Table 3, together with the conditions in which they have been determined. Within the error of the experiments, the activation energy does not vary with the initial pressure. This behaviour is in contrast with that shown by the normal paraffins (Ingold, Stubbs, and Hinshelwood, *Proc. Roy. Soc.*, 1950, *A*, **203**, 487).

Effect of Added Gases.—A number of experiments have been carried out in which nitric oxide or lower olefins have been added to the olefin under study to see whether or not they show an inhibitory effect. The results are collected in Table 4.

TABLE 3. *Activation energies.*

	Range of temp.	Press., mm.	kcal./ g.-mol.		Range of temp.	Press., mm.	kcal./ g.-mol.
But-1-ene	490—600°	100	66·4	2-Methylbut-1-ene	520—570	100	62·8
But-2-ene	540—590	100	57·4			300	61·5
		300	55·6	3-Methylbut-1-ene	510—570	100	65·0
*iso*Butene	580—630	100	53·3			300	61·8
Pent-1-ene	430—530	100	53·1	Hex-1-ene	460—530	100	53·3
		300	54·6	Hept-1-ene	450—510	100	49·0

TABLE 4. *Effect of added gases on the decomposition rate of various olefins.*

	Nitric oxide	Ethylene	Propylene	But-1-ene
Propylene	acceln.	—	—	—
But-1-ene	acceln.	slight decrease	none	—
But-2-ene	acceln.	—	—	—
*iso*Butene	none	—	—	—
Pent-1-ene	none	slight decrease	slight decrease	—
2-Methylbut-1-ene	none	slight decrease	slight decrease	—
3-Methylbut-1-ene	slight acceln.	slight decrease	slight decrease	none
Hex-1-ene	none	none	none	none
Hept-1-ene	none	none	none	none

Analytical Results.—Table 5 shows the results of the analyses (carried out with a Bone and Wheeler apparatus) of samples taken at different times during the decomposition of 200 mm. of hex-1-ene and of hept-1-ene. For both, the plot of the amount of each of the different products against time shows the same general shape as the Δp–time curve.

TABLE 5. *Reaction products from hex-1-ene and hept-1-ene.* (*Initial press.*, 200 *mm.*).*

	Hex-1-ene, 500°				Hept-1-ene, 510°			
Total press. in reaction vessel before sampling	225	250	280	300	225	250	275	300
Δp	25	50	80	100	25	50	75	100
Press. of sample	43	72·5	113	152	39	70	105	111
Ethylene	13	20	34	48	18	24	44	39
Other olefins	19	28	42	54	7	20	27	32
Saturated hydrocarbons + hydrogen	11	25·5	37	50	14·5	26	34	40
Contraction after explosion	28·5	58	69·5	104	28	50	66	68
CO_2 from explosion	22	55	51	77	20	38	43	49

TABLE 6. *Reaction products from* isobutene *at* 580° (*initial press.*, 200 *mm.*).*

Δp	H_2 formed	CH_4 formed	C_3H_6 formed	C_2H_4 formed	*iso*Butane formed	*iso*Butene reacted	Other products formed	Condensed	C_3H_8 formed
2	2·44	4·6	3·17	0	1·17	32	1·2	30	0
5	4·17	6·77	4·67	3·74	1·64	35·7	3	24	0
10	6·30	11·2	6·75	1·89	2·52	35	7	20	0
20	9·92	19·5	9·88	3·87	3·68	64	14	44	0
40	19·4	38·1	14·7	13·1	5·17	104	30	67	0

* All pressures are expressed in mm. of mercury.

In Table 6 are included the results of analyses (carried out in a mass spectrometer) of samples taken at different times from the decomposition of 200 mm. of *iso*butene. Similar analyses from experiments made with the addition of 20 mm. of nitric oxide have been made, and it has been shown that the products of the pyrolysis of *iso*butene have the same composition, with or without nitric oxide.

DISCUSSION

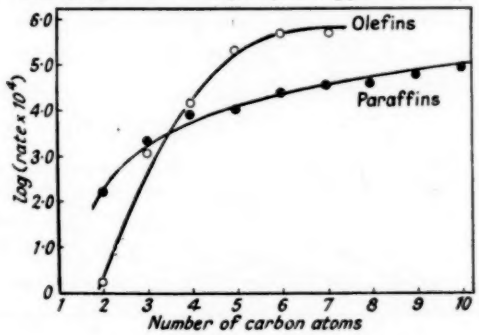
Number of Carbon Atoms.—Owing to the various difficulties described previously, the analytical results are unfortunately not precise enough to define the exact reaction mechanism for the whole series of olefins. For propylene it has been shown that the reaction proceeds by a number of steps, and, as will be discussed later, the results for *iso*butene indicate a similar mechanism. For the other olefins also the reaction will

probably go by a series of steps. In general, in such a case the velocity constant and activation energy measured will be a function of the velocity constants of the different steps. In the present example, however, it is difficult to account for a *first-order* reaction leading to considerable polymerization, unless the rate is chiefly governed by a primary step involving decomposition. If this is so, then the measured activation energy will refer to this step.

Fig. 3 shows the plot of log rate against the number of carbon atoms for the series of straight-chain Δ^1-olefins, together with a similar plot for the nitric oxide-inhibited decomposition of the normal paraffins (for comparison the nitric oxide-inhibited reaction of the latter must be used, since this is believed to be the molecular decomposition process). It is seen that for the olefins, there is initially a much more rapid increase of rate with the number of carbon atoms than for the paraffins.

The curves cross between C_3 and C_4 and it is interesting to consider the reason for this. Ethylene and propylene decompose more slowly than the corresponding paraffins, and neither has a C–C bond β to the double bond. It has been stated as a general rule that when there is a doubly bonded carbon atom in a molecule, the bonds in the α-position to this bond are stronger than normal, whereas those in the β-position are weaker (Rice and Rice, " The Aliphatic Free Radicals "). Thus the absence of the β-bond in ethylene and

FIG. 3. *Relative reaction rates for members of the normal paraffin series and straight-chain Δ^1-olefins* (530°; p_0 = 100 *mm.*).



propylene would mean a bigger activation energy for the initial step and a consequent diminution in the rate. The higher olefins having a C–C bond in the β-position to the double bond, it might be argued that the decomposition rate would be greater than with the corresponding paraffin. This explanation is however doubtful, since Stevenson's results (Steacie, " Atomic and Free Radical Reactions ") on the α-bonds in olefins do not appear to show a strengthening compared with the bond in the corresponding paraffin.

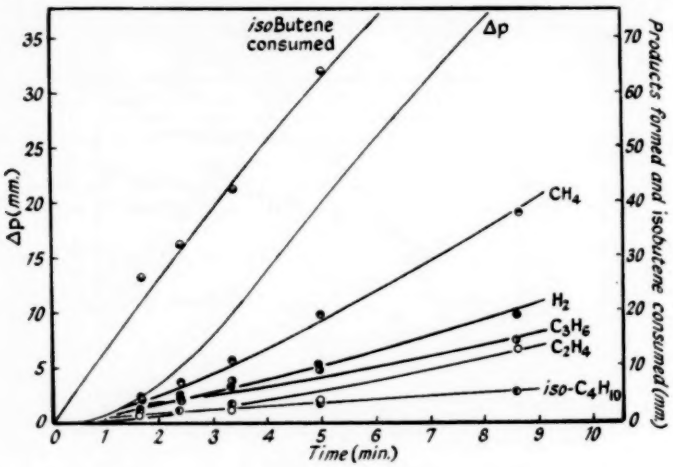
Activation Energy.—An inspection of the activation-energy values in Table 3 makes possible a certain classification of the olefins. If *iso*butene is considered as a substituted propylene, we can say that the substitution of a $C_{(2)}$-hydrogen atom by a methyl group diminishes the activation energy (propylene, 57; *iso*butene, 53). Comparing now but-1-ene with its 2- and its 3-methyl-substituted compounds, it appears that the substitution of the $C_{(2)}$-hydrogen atom of but-1-ene by a methyl group produces a diminution of the activation energy similar to that observed in propylene and *iso*butene (but-1-ene, 66·4; 2-methylbut-1-ene, 62). On the other hand, the substitution of a $C_{(3)}$-hydrogen atom of but-1-ene by a methyl group produces a very small diminution of the activation energy (but-1-ene, 66·4; 3-methylbut-1-ene, 64). Comparison of the two linear butenes shows that but-2-ene has a lower activation energy (but-1-ene, 66·4; but-2-ene, 56·5).

Consideration of the linear Δ^1-olefins from butene upwards shows a decrease in activation energy as the series is ascended. For a particular olefin, however, the activation energy does not vary with the pressure, in contrast to the behaviour observed with the nitric oxide-inhibited decomposition of the normal paraffins.

Number of Degrees of Freedom.—According to conventional methods the minimum number of degrees of freedom (n) among which E must be distributed to account for the absolute rate, has been calculated for each olefin, and the results are collected in Table 7. They have all been calculated for 200 mm. pressure, because in this region of pressure the transition from the first to the second order appears to be in progress. The molecular diameter has been assumed to be the same for all the olefins, *viz.*, 5×10^{-8} cm.

In the calculation of the absolute velocity (molecules per c.c. and sec.) the ratio of Δp to amount of olefin used has been assumed equal to two. In the case of *iso*butene, analysis has proved this to be true. Direct determination for the other olefins has not been possible although the values of m in Table 2 are between 1 and 2. In any case, a great variation of m is necessary to change the number of degrees of freedom required to account for the observed rates. The values in Table 7 can therefore be accepted as very probable ones, and the number of degrees of freedom is seen in every case to be plausible, having regard to the formulæ of the olefin molecules.

FIG. 4. *Thermal decomposition of* 200 *mm. of* isobutene *at* 580°; *variation of reaction products with time.*



Mechanism of Reaction.—The analytical results for the higher olefins studied in the present work (hex-1-ene and hept-1-ene) are not complete enough to justify detailed conclusions regarding the mechanism of decomposition. Consideration of this will therefore be restricted to *iso*butene, where mass-spectrometric analyses have provided fuller information.

According to the experimental results in Table 6, in the decomposition of *iso*butene at 580°, the products are to a considerable extent polymers, most of which condense on

TABLE 7. *Degrees of freedom required to account for reaction rate.*

Olefin	Temp.	n	Olefin	Temp.	n	Olefin	Temp.	n
But-1-ene.....	530°	9	Pent-1-ene	470°	5	Hex-1-ene	470°	5—6
But-2-ene.....	530	4	2-Methylbut-1-ene...	530	8	Hept-1-ene	470	4
*iso*Butene.....	580	2	3-Methylbut-1-ene...	530	9			

sampling. Up to 50% of decomposition, less than 47% of the carbon atoms and less than 32% of the hydrogen atoms can be accounted for, the rest being lost by condensation.

The Δp–time curve for *iso*butene (Fig. 4) shows an upward curvature before the maximum rate is obtained, and it appears that, as for propylene, there are at first reactions of *iso*butene without change of pressure, giving intermediate compounds which subsequently decompose.

It is important to know the relative amounts in which products are produced at zero time. For this purpose, the values of Table 8 have been calculated from the experimental values of Table 6 and the extrapolation to zero time gives the values of the last row. All products have been referred to methane, since this does not decompose at 580°, whereas propylene and *iso*butane decompose appreciably, producing the variation with time that is observed in the ratios given in Table 8.

TABLE 8. *Ratios of analytical products.*

Time	CH_4/C_3H_6	CH_4/C_2H_4	CH_4/H_2	CH_4/*iso*Butane	H/C (cond. prod.)
1′ 36″	1·4	—	1·8	3·9	1·8
2′ 18″	1·4	1·8	1·7	4·1	1·7
3′ 18″	1·6	5·9	1·8	4·4	1·7
4′ 48″	1·9	5·0	1·9	5·3	1·6
8′ 30″	2·5	2·9	1·9	7·3	1·5
0 (extr.)	1	7·5	1·85	3·0	1·9

Since there has been no analysis of the condensed products themselves, only a tentative mechanism can be proposed. Any mechanism for the decomposition of *iso*butene under the conditions of this work must take into account three factors: (1) More than 50% of the *iso*butene used forms polymers; (2) a "lag" in the Δp–time curve; (3) the extrapolated relations of Table 8.

These facts being considered in relation to the mechanism already proposed for propylene, there are two different possibilities for the primary breaking of the molecule of *iso*butene that account for them, *viz.*, the breaking into two radicals:

$$(CH_3)_2C{:}CH_2 \longrightarrow CH_3 + C_3H_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or the breaking and transfer of a hydrogen atom by molecular rearrangement:

$$(CH_3)_2C{:}CH_2 \longrightarrow CH_4 + C_3H_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In case (1) subsequent steps will be the immediate reaction of each radical with a molecule of *iso*butene, giving methane and propylene respectively:

$$(CH_3)_2C{:}CH_2 + CH_3 \longrightarrow CH_4 + C_4H_7$$
$$(CH_3)_2C{:}CH_2 + C_3H_5 \longrightarrow CH_3{\cdot}CH{:}CH_2 + C_4H_7$$

If we assume that the two C_4 radicals polymerise to form a C_8 compound, these steps would be summed up as follows:

$$3\ \textit{iso}\text{Butene} \longrightarrow CH_4 + C_3H_6 + C_8H_{14} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If we suppose that the first step is (2), the molecule C_3H_4 can abstract two atoms of hydrogen from two molecules of *iso*butene, and the overall sum of the steps gives the same reaction (3): $(CH_3)_2C{:}CH_2 + C_3H_4 \longrightarrow C_4H_7 + C_3H_5$; $(CH_3)_2C{:}CH_2 + C_3H_5 \longrightarrow C_4H_7 + CH_3{\cdot}CH{:}CH_2$.

The extrapolated values in Table 8 justify equation (3): methane and propylene can be considered as the stable primary products in equal proportion. Ethylene is a product in the decomposition of propylene, and *iso*butane is obviously a secondary product formed by hydrogenation of *iso*butene. Hurd and Blunk (*loc. cit.*) found under very similar conditions that the primary products were methane and propylene. Extrapolation to zero conversion was shown to be not very efficient for the identification of primary products, since ethylene, which needs the breaking of two bonds and is a secondary product, does not disappear at zero conversion, either in their experiments or in the present work.

The polymer in equation (3) can subsequently decompose giving hydrogen and methane, or can combine with more *iso*butene or propylene to give higher polymers. The last column in Table 8 shows that the relation H/C in the polymer diminishes with time.

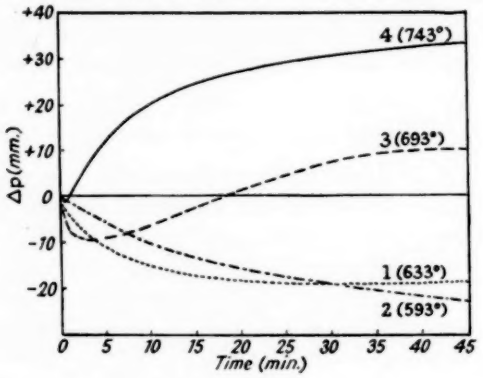
A criterion frequently used to decide upon the intervention of radicals is the use of nitric oxide, which is an inhibitor of chain reactions. In the case of *iso*butene, added nitric oxide has no effect either on the Δp–time curve or on the decomposition products. This is, however, to be expected since other olefins like propylene are inhibitors of chain reactions and it has been shown that *iso*butene is an inhibitor of the decomposition of

pentane. Thus there is still the uncertainty of the primary breaking of the molecule of *iso*butene. Eltenton (*J. Chem. Phys.*, 1942, **10**, 403; 1947, **15**, 465), using a mass spectrometer, concluded that propylene reacts more easily than nitric oxide with methyl radicals, and that at high temperatures methyl and allyl radicals can be detected in the decomposition of propylene. In mechanism (1) all steps are chain-ending and so the effect of nitric oxide would be very limited.

Ethylene.—The pyrolysis of ethylene differs from that of the higher olefins in many respects and for this reason the following brief study is recorded separately. Many papers have been published on the thermal decomposition of ethylene including the following: Frey and Smith, *Ind. Eng. Chem.*, 1928, **20**, 948; Hurd, *ibid.*, 1934, **26**, 50; Burnham and Pease, *J. Amer. Chem. Soc.*, 1942, **64**, 1404; Pease, *ibid.*, 1930, **52**, 1158; Burk, Baldwin, and Whitacre, *Ind. Eng. Chem.*, 1937, **29**, 326; Storch, *J. Amer. Chem. Soc.*, 1934, **56**, 374; 1935, **57**, 2598; Wheeler and Wood, *ibid.*, 1930, **52**, 1823; Zanetti, Suydam, and Offner, *ibid.*, 1922, **44**, 2036; Schneider and Frolich, *Ind. Eng. Chem.*, 1931, **23**, 1405; Tropsch, Parrish, and Egloff, *ibid.*, 1936, **28**, 581.

General form of the Δp*–time curves.* The change in pressure of 200 mm. of ethylene at different temperatures is shown in Fig. 5. At the lower temperatures there is a decrease

FIG. 5. Δp*–time curves for the pyrolysis of* 200 *mm. of ethylene at various temperatures.*



in pressure which, according to previous investigations, can be ascribed to polymerization of ethylene. At higher temperatures, the initial decrease in pressure is followed by an increase, and at about 700°, the form is as in the typical example of curve 3 in Fig. 5. On further increase of temperature, the initial decrease gradually disappears and near 800° only an increase of pressure is observed. This gradual change in the form of the Δ*p*–time curve indicates that decomposition predominates at higher temperatures.

Order of reaction. The rate of polymerization (as determined by the initial slope of the Δ*p*–time curve at lower temperature) was determined at pressures from 50 to 500 mm. at several temperatures (623°, 643°, 663°, 683°, 713°). The reaction was found to be exactly of the second order at each temperature.

The rate of decomposition [as determined by the tangent to the Δ*p*–time curve at higher temperatures, or the tangent where Δ*p* becomes positive for curves of type 3 (Fig. 5)] was determined at 10°-intervals from 713° to 783° with initial pressures from 50 to 500 mm. The reaction was of the first order up to 250 mm. but at higher pressures the order increased towards 2.

Activation energy. In Fig. 6 the values of log (rate) for the two processes (polymerization and decomposition) are plotted at different pressures. For the polymerization, the activation energy is independent of the pressure and the value of 34·6 kcal. determined agrees very well with that of Pease (*J. Amer. Chem. Soc.*, 1931, **53**, 613).

The activation energy for the decomposition seems to vary with pressure and the values are recorded in Table 9. The plot of activation energy against pressure is a straight

line which on extrapolation to zero pressure gives a value of 75 kcal./g.-mol. Since the polymerization is of second order, it may well be that at higher pressures the observed decomposition rate is a function of the two processes and the value of 75 kcal. may be regarded as a minimum for the activation energy of decomposition.

It is observed in Fig. 6 that around 710° the plot of log (rate) against $1/T$ is no longer a straight line. It is at this temperature that the Δp–time curves are of type 3 (Fig. 5), and obviously the rates of polymerization and decomposition are nearly equal.

FIG. 6. *Plot of log (rate) against* 1/T *for ethylene at various pressures.*

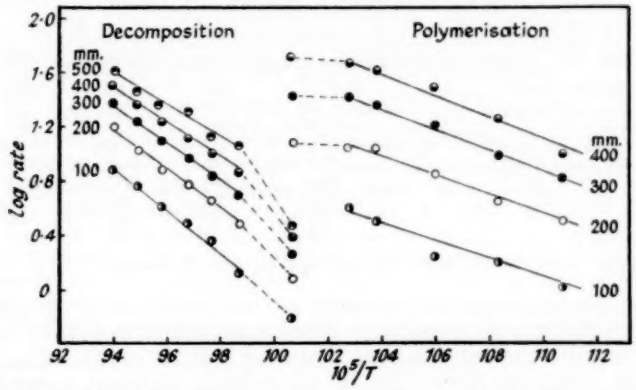
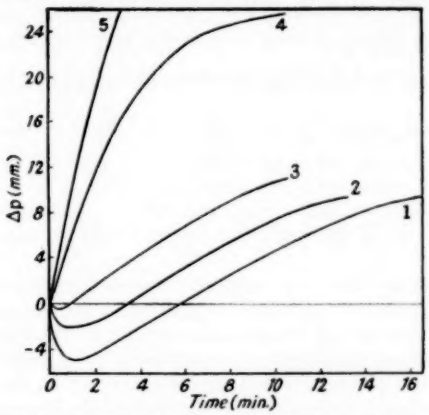


FIG. 7. ***Influence of nitric oxide on the*** Δp–*time curve for the pyrolysis of* 200 *mm. of ethylene at* 713°.



Curve 1 : *no* NO. *Curve* 2 : 50 *mm.* NO. *Curve* 3 : 13·0 *mm.* NO. *Curve* 4 : 5·0 *mm.* NO. *Curve* 5 : 96·0 *mm.* NO.

Effect of nitric oxide. Experiments carried out at 623° showed that when the Δp–time curves are of type 1 or 2 (Fig. 5), nitric oxide decreases the polymerization rate as shown in Table 10. At intermediate temperatures (713°) when the Δp–time curves are of type 1 (Fig. 7), small amounts of nitric oxide reduce the polymerization rate without affecting the decomposition (2, 3). With larger amounts of nitric oxide no decrease of pressure is observed at all, and the decomposition rate is increased (4, 5). This same accelerating effect is found at 773°.

TABLE 9. *Activation energy of ethylene decomposition.*

Press., mm. Hg	500	400	300	200	100
Act. energy, kcal./g.-mol.	57·8	62·4	64·5	68·3	70·6

TABLE 10. *Effect of nitric oxide on the rate of polymerization of ethylene.*

	Ethylene : 210 mm.		Temp. : 623°		Ethylene : 200 mm.		Temp. : 773°	
NO, mm. Hg	0	3·5	13·5	51·5	78·5	0	3	9	22
Rate, mm. Hg/min.	2·8	2·2	1·1	0·3	−0·15	9·8	12	14·4	30

Analytical results. Analyses were made (on a Bone and Wheeler apparatus) of the decomposition products from 200 mm. of ethylene. The results at 773° are recorded in Table 11. From the values of contraction and carbon dioxide produced in explosion the "saturated hydrocarbons plus hydrogen" appears to be exclusively methane and hydrogen.

TABLE 11. *Analysis of products from* 200 *mm. of ethylene at* 773°.*

Total press. reaction vessel	205	210	220	230	240
Δp	5	10	20	30	40
Ethylene used	123·5	131	152·15	166	170
Unsaturated	4	1	1·6	1·6	0
Satd. hydrocarbons + hydrogen	102	130	164	190	208
Contraction (after expl.)	182	234	308	333	357
CO_2 (from expl.)	65·7	83	94	98	110
CH_4	65·7	83	94	98	110
H_2	36·3	47	70	92	98

* All pressures are expressed as mm. of mercury.

The percentages of carbon and hydrogen not accounted for in the gaseous product are recorded in Table 12. The percentage of carbon accounted for remains fairly constant, but that of hydrogen decreases with time, indicating that the condensed product is losing hydrogen. The carbon/hydrogen ratio of the polymer therefore increases with time, and ultimately it would probably lose all its hydrogen, leaving only carbon. At this high temperature (773°) the products of the polymerization obviously decompose, and in fact the reaction vessel is quickly coated with a thin layer of carbon.

TABLE 12. *Percentages of carbon and hydrogen* not *accounted for in gaseous product.*

Δp, mm. Hg	5	10	20	30	40
% C not accounted for	73	68	68	74	67
% H not accounted for	32	18	15	13	6
C/H in condensed product	1·1	1·8	2·2	2·6	5·2

Analyses were also made at 733°, 693°, and 623°. At each temperature the amount of carbon dioxide produced in the explosion showed that in addition to methane higher paraffins are produced.

At the lower temperature (623°) the ethylene is consumed according to a second-order equation, but gaseous products (paraffins + hydrogen) are found in the decomposition products, 30% of the carbon atoms being accounted for in the gaseous phase.

Conclusion.—The major question which arises from the foregoing experimental results for ethylene is whether the polymerization and decomposition are simultaneous processes or whether polymerization occurs first and is followed by the decomposition of the polymer formed.

The following facts are in favour of consecutive processes: At the lower temperatures (623°) the ethylene is used up according to a second-order equation, but gaseous products (paraffins plus hydrogen) are found in the decomposition products, 30% of the carbon atoms being accounted for in the gaseous phase. The activation energy for decomposition varies with pressure, giving an extrapolated value of 75 kcal./mol. at zero pressure. There is a production of both polymer and gaseous products at all temperatures studied, and it has been proved that the polymer decomposes at 773° becoming poorer in hydrogen.

The effect of nitric oxide is more suggestive of simultaneous processes. Its inhibitory effect on the polymerization probably means that it reacts with radicals and thereby breaks chains. If under the action of nitric oxide no polymer is formed, none could decompose, so that the decomposition process would automatically be inhibited. This does not happen and thus simultaneous processes are indicated. This conclusion is

however, rendered somewhat uncertain in so far as the acceleration produced by nitric oxide might be due to an actual oxidation of ethylene.

The authors thank Sir Cyril Hinshelwood, F.R.S., for much valuable advice in connection with this work, also Mr. I. A. H. Henderson and Dr. C. J. Danby for carrying out the analyses with the mass spectrograph. The olefins obtained from the National Bureau of Standards were the gift of the Rockefeller Foundation, New York.

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76. *Studies of the Structure of Emetine. Part V.* The Structure of the Rubremetinium Salts.*

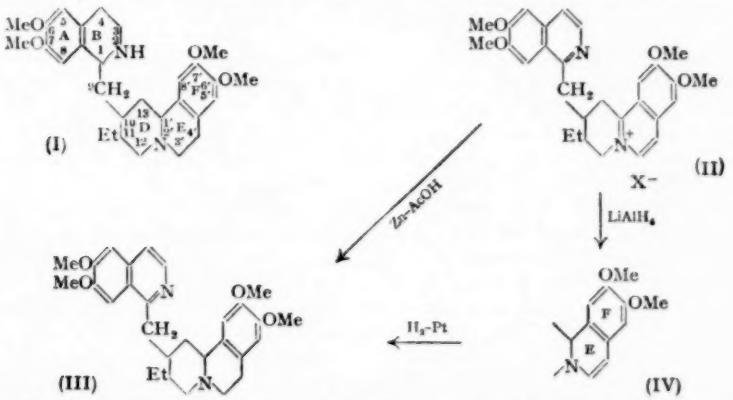
By H. T. OPENSHAW and H. C. S. WOOD.

Catalytic hydrogenation of rubremetinium chloride produces two stereoisomeric dihydrorubremetines, which exhibit pyrrole colour reactions and are readily re-oxidised to rubremetinium chloride. The constitution of the rubremetinium salts is discussed in the light of these observations, of their previously described reactions, and of the course of the dehydrogenation of emetine, and it is concluded that they are most adequately represented by the structure (V) (Battersby, Openshaw, and Wood, *Experientia*, 1949, **5**, 114). The structures of *O*-methylpsychotrine and tetradehydroemetine are also discussed, that of the former being revised to (VII).

THE establishment of the structure (I) for emetine necessitates a reconsideration of the constitution of the highly coloured rubremetinium salts, which are formed by treating the alkaloid with mild acidic oxidising agents such as ferric chloride, bromine, iodine, or mercuric acetate (Carr and Pyman, *J.*, 1914, **105**, 1591; Karrer, *Ber.*, 1916, **49**, 2057; Battersby and Openshaw, Part II, *J.*, 1949, S 67). The reaction involves the removal of eight hydrogen atoms and the formation of a salt of a monoacidic, quaternary base, according to the equation:

$$C_{29}H_{40}O_4N_2 - 8H + HX = C_{29}H_{33}O_4N_2X$$

Three different structures have been put forward for these salts.† The first, due to Brindley and Pyman (*J.*, 1927, 1067), was based on an incorrect emetine formula and need



not be considered further. The second was proposed by Karrer, Eugster, and Rüttner (*Helv. Chim. Acta*, 1948, **31**, 1219), who considered that the oxidation involves the aromatis-

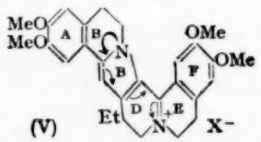
* Part IV, *J.*, 1949, 3207.

† Pyman designated these substances as salts of a hypothetical anhydro-base, $C_{29}H_{32}O_4N_2$, which he named "rubremetine"; it is convenient to retain this name as a generic term for the rubremetinium salts. Karrer preferred the name "dehydroemetine."

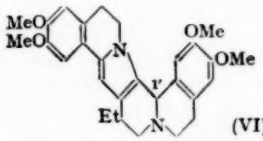
ation of rings B and E, leading to the structure (II). This suggestion was based largely on the reduction of rubremetine by zinc and acetic acid to a crystalline, optically active tetrahydro-derivative which was resistant to catalytic hydrogenation. This behaviour was ascribed to the known ease of reduction of a quaternary *iso*quinolinium system (ring E) and the contrasting resistance to reduction of a non-quaternised *iso*quinoline (ring B); the reduction product was assigned the structure (III). Since this structure had already been assigned to the minor alkaloid emetamine, the tetrahydro-compound was assumed to be a stereoisomer of emetamine. On this view, it would be expected that emetamine should also yield rubremetine on oxidation. However, Karrer, Eugster, and Rüttner confirmed, by absorption-spectrum measurements, the earlier statement of Brindley and Pyman (*loc. cit.*) that the oxidation product of emetamine, although coloured and quaternary, is not identical with rubremetine. This observation, and the failure of the structure (II) to account for the lack of basicity of the non-quaternary nitrogen atom and for the intense colour of the salts, seem to provide sufficient grounds for the rejection of the Karrer proposal.

Recently, however, Karrer and Rüttner (*Helv. Chim. Acta*, 1950, **33**, 291) have brought forward further evidence which they consider to indicate the presence in rubremetine of a quaternary *iso*quinolinium system. On treatment with lithium aluminium hydride, rubremetinium bromide yielded a crystalline, very unstable compound analysing as a dihydrorubremetine, $C_{29}H_{34}O_4N_2$. By analogy with the similar reduction of simple *iso*quinolinium salts this product was assigned the partial structure (IV). On catalytic hydrogenation it absorbed one mol. of hydrogen to give a mixture of two supposed tetrahydrorubremetines, one of which was identical with that obtained by zinc dust reduction of rubremetine. The second product was characterised by an exceptionally large lævorotation ($[\alpha]_D$ −380°); both products had identical ultra-violet absorption spectra.

In an attempt to overcome the various objections to the structure (II), Battersby, Openshaw, and Wood (*Experientia*, 1949, **5**, 114) advanced an alternative, mesomeric structure (V), which is similar to that of a cyanine dye, the single positive charge being



(V)

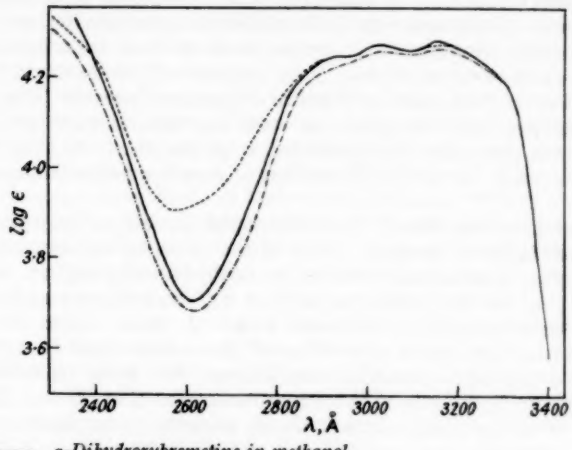


(VI)

shared between the two nitrogen atoms. This structure is consistent with the intense colour of the substance, with its behaviour as a monoacidic, quaternary base, and with the formation of a different product by the oxidation of emetamine. The structure (V) contains a pyrrole nucleus and we found that the crude product of zinc dust reduction of rubremetine gives pyrrole colour reactions. A further study of the reduction of rubremetine has provided additional support for the structure (V).

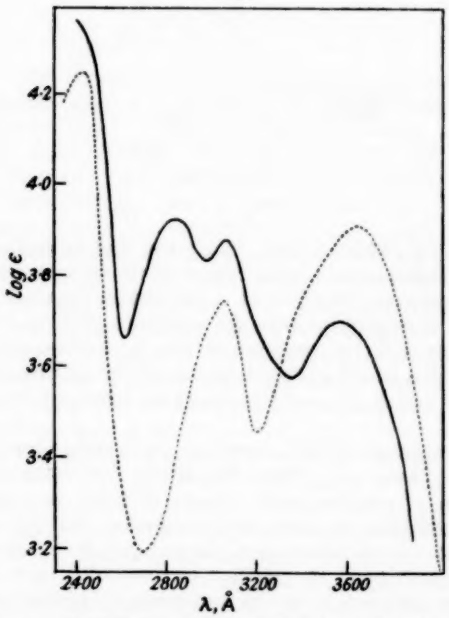
On hydrogenation of rubremetinium chloride in ethanol, in the presence of sodium acetate and platinic oxide, 1·0 mol. of hydrogen is absorbed and the solution becomes colourless. Although the product is readily re-oxidised by air in the presence of the catalyst (Part II, *loc. cit.*), it is relatively stable when the platinum is removed. It consists of a mixture of two stereoisomeric dihydrorubremetines, the α-isomer being strongly lævorotatory ($[\alpha]_D$ −395°) and the β-isomer even more strongly dextrorotatory ($[\alpha]_D$ +406°). When the original mixture is crystallised from methanol, a partial racemate separates as a very sparingly soluble methanol complex containing one molecule of each isomer and two molecules of methanol, and having m. p. 128° and $[\alpha]_D$ +21°. From the mother-liquor, the pure α-isomer (m. p. 198°) is obtained. The complex splits up on crystallisation from ethanol, and the less soluble β-isomer (m. p. 202°) separates first. If methanol solutions of the two pure isomers are mixed, the partial racemate is again precipitated. The relation between these two isomers thus resembles very closely that of a pair of enantiomorphs; they have opposite and nearly equal rotations, they have

FIG. 1.



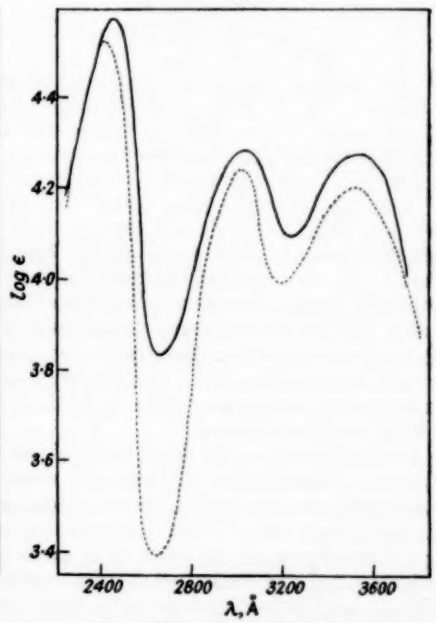
——— *α-Dihydrorubremetine in methanol.*
– – – – – *β-Dihydrorubremetine in methanol.*
—·—·—·— *" Tetrahydro- and isotetrahydro-dehydroemetine " (Karrer and Rüttner).*

FIG. 2.

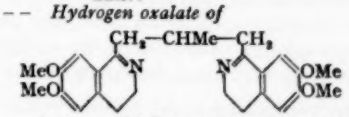


——— *O-Methylpsychotrine hydrogen oxalate in ethanol.*
– – – – *Hydrochloride of 3:4-dihydro-1-methyl-6:7-methylenedioxy- or 1-benzyl-3:4-dihydro-6:7-methylenedioxy-isoquinoline in ethanol (Bills and Noller).*

FIG. 3.



——— *Tetradehydrometine hydrogen oxalate in water.*
– – – – *Hydrogen oxalate of*

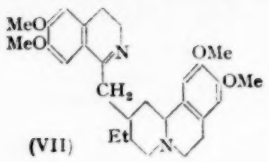


in water (McIntyre, Openshaw, and Wood).

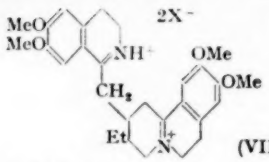
nearly equal melting points, and they form a molecular complex analogous to a racemate. However, they differ sufficiently in solubility to admit of their separation.

Both the isomeric dihydrorubremetines exhibit the pine-shaving reaction, give a green colour with Ehrlich's reagent, and couple with sodium diazobenzene-*p*-sulphonate; emetine shows none of these reactions. Potentiometric titration shows them to be monoacidic bases. They possess almost identical absorption spectra (Fig. 1). They resist further hydrogenation, and on oxidation with mercuric acetate are reconverted into rubremetine. These properties are consistent with the structure (VI), the formation of two stereoisomers being due to the formation of a new asymmetric centre ($C_{(1')}$) in the reduction.

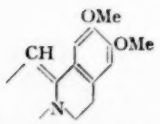
Some support for the structure (V) for rubremetine can also be gained by a consideration of the course of oxidation of emetine. Most of the oxidising agents used are known to be capable of converting a tetrahydro- into a 3 : 4-dihydro-*iso*quinoline. Pyman (*J.*, **1917**, **111**, 419) showed that the first oxidation product is *O*-methylpsychotrine, which he formulated as a 1 : 9-dehydroemetine. Bills and Noller (*J. Amer. Chem. Soc.*, **1948**, **70**, 957) have shown, however, that the 1 : 2-position of the double bond is strongly favoured in 1-substituted 3 : 4-dihydro*iso*quinoline derivatives. We have therefore measured the ultra-violet absorption spectrum of *O*-methylpsychotrine (Fig. 2) and find that it corresponds with the structure (VII), since it shows maxima corresponding both to those of the 3 : 4-dihydro*iso*quinoline system (rings A and B) and to those of the tetrahydro*iso*-



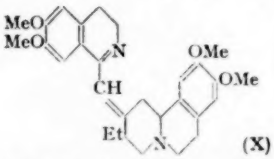
(VII)



(VIII)



(IX)



(X)

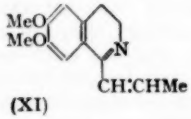
quinoline system (rings E and F) (cf. Part I, *J.*, **1949**, S 59). Battersby and Openshaw (Part II, *loc. cit.*) isolated the base tetradehydroemetine as the product of the second stage of the oxidation. The structure of this substance is still uncertain. Its salts are reasonably stable, and the most natural assumption is that they possess the structure (VIII); the ultra-violet absorption spectrum is consistent with the presence of two 3 : 4-dihydro*iso*quinoline nuclei (Fig. 3).* The free base, which would in this case possess the alternative double bond arrangement (IX), is much less stable, as would be expected from the work of Bills and Noller (*loc. cit.*).

Doubt is cast on the correctness of the structure (VIII), however, by certain observations by Hazlett and McEwen (*J. Amer. Chem. Soc.*, **1951**, **73**, 2578), who have reinvestigated the mercuric acetate oxidation of emetine, with results differing in some respects from ours. They obtained, in addition to tetradehydroemetine (32%), an approximately equal quantity of a more stable, isomeric base, *iso*tetradehydroemetine (28% yield). The formation of this new isomer must be ascribed to some difference in reaction conditions, since we have never encountered it in the numerous oxidations we have carried out, in spite of a careful search for other products, and in recent experiments approximately 90% of the original emetine has been accounted for as tetradehydroemetine or rubremetine. That the new base cannot be merely a stereoisomer of (VIII), differing from tetradehydroemetine in the configuration of one or both the remaining asymmetric centres ($C_{(10)}$ and $C_{(11)}$), is shown by the formation of emetine from both isomers by hydro-

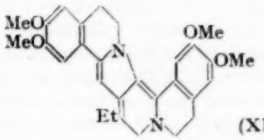
* Redetermination shows that the values of the extinction coefficients given in Part II are too low, but the positions of the maxima are substantially confirmed.

genation. We have obtained only *iso*emetine (isolated in 78% yield as the benzoyl derivative) by the hydrogenation of an aqueous solution of tetradehydroemetine hydrogen oxalate, but Hazlett and McEwen, using an alcoholic suspension of the salt, obtained a little emetine and *iso*emetine, and much larger amounts of two new stereoisomers of emetine; hydrogenation of *iso*tetradehydroemetine gave emetine as the only isolable product. The very close similarity of the absorption spectra of the two isomeric tetradehydroemetines makes it unlikely that they differ in the positions of their double bonds, and the foregoing observations are most readily interpreted by formulating the two bases as the *cis*- and the *trans*-isomer of a conjugated structure (X) similar to that proposed in Part II. The remarkably close correspondence of their absorption spectra with that of a synthetic bis-3 : 4-dihydro*iso*quinoline (Fig. 3) must then be dismissed as fortuitous, however. An attempt to synthesise 3 : 4-dihydro-6 : 7-dimethoxy-1-propenyl*iso*quinoline (XI) for spectral comparison has so far failed in its object, as it has not been found possible to purify the product owing to its instability.

No further intermediate stages in the oxidation of emetine to rubremetine have been isolated, but it is possible that the next step involves attack on $C_{(13)}$, which is activated either by the $C{=}N^+$ group (structure VIII) or by the conjugated system (structure X); removal of a hydrogen atom and an electron would be followed by cyclisation, giving respectively a dihydropyrrole derivative or dihydrorubremetine (VI), either being readily dehydrogenated to rubremetine.



(XI)



(XII)

The structure (V) for rubremetine has been criticised by Karrer and Rüttner on the grounds that it contains two dihydropyridine rings (D and E) which should be highly susceptible to oxidation. Ring E, however, as represented in structure (V), forms part of a 3 : 4-dihydro*iso*quinoline system, the stability of which is well known. Dehydrogenation of such a structure cannot normally be achieved by the action of halogens (see, for example, Leonard and Leubner, *J. Amer. Chem. Soc.*, 1949, **71**, 3408), and we have found that hot aqueous mercuric acetate is also ineffective. Ring D is fused to a pyrrole ring and thus forms a system not unlike that present in the alkaloid harmaline; moreover, the molecule probably gains additional stability from its resonance-hybrid character.

Karrer and Rüttner also consider that the structure (V) is inconsistent with their observations on the reduction of rubremetine with lithium aluminium hydride. It should, however, be pointed out that their interpretation of this reaction is open to question. Reduction of (II) to the dihydro-derivative (IV) introduces a new asymmetric centre, but only one crystalline product was isolated. The further hydrogenation of this apparently homogeneous product gave rise to two stereoisomeric tetrahydro-compounds, although no new asymmetric centre is formed in this reaction. It may be significant that these two products have absorption spectra identical with that of α-dihydrorubremetine (Fig. 1), and that one of them ("*iso*tetrahydrodehydroemetine") resembles this substance also in its melting point and in its exceptionally high lævorotation. The analytical figures given for this product also agree more closely with those of a dihydrorubremetine.

Hazlett and McEwen (*loc. cit.*) have obtained an optically inactive base having an absorption spectrum similar to that of dihydrorubremetine, by the hydrogenation of an unstable, crystalline "dehydrohalorubremetine" produced by treatment of rubremetinium chloride with alkali. Although they designate this product as a tetrahydro-compound, they admit that this designation is insecurely based, since the hydrogenation was carried out on crude material. It seems probable to us that the substance is a racemic dihydrorubremetine (VI) and that the dehydrohalorubremetine from which it is derived has the structure (XII), in which the sole remaining asymmetric centre of rubremetine has been destroyed.

It thus appears to us that the majority of the properties and reactions of the rubremetinium salts can be best explained on the basis of structure (V). Since this structure contains only one asymmetric centre ($C_{(11)}$) whereas emetine contains four, the rubremetinium salts should prove convenient transformation products through which synthetic ipecacuanha alkaloids of unknown or mixed stereochemical configuration may be compared with the natural materials. (±)-Rubremetinium bromide has already been obtained (Battersby and Openshaw, *Experientia*, 1950, **6**, 378) by the dehydrogenation of a synthetic base of structure (VII), and in order to facilitate the eventual resolution of such a product, we have prepared some diastereoisomeric salts of (+)-rubremetine.

Experimental

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Absorption spectra were measured on a " Unicam " S.P. 500 Spectrophotometer.)

Mercuric Acetate Oxidation of Emetine.—The original procedure (Part II, *loc. cit.*) has been slightly modified to increase the total yield of oxidation products. A solution of mercuric acetate (61·9 g.), potassium acetate (6·2 g.), and acetic acid (25 ml.) in water (550 ml.) was added during 1 hour to a hot solution of emetine hydrochloride heptahydrate (20 g.) in water (240 ml.); the mixture was heated for a further 2 hours at 100°, cooled, filtered from mercurous acetate, and freed from dissolved mercury salts with hydrogen sulphide as described previously. The combined filtrate and washings were concentrated to 400 ml., treated with concentrated hydrochloric acid (20 ml.), and cooled slowly, whereupon the bulk of the rubremetinium chloride crystallised. The filtrate was made strongly alkaline with sodium carbonate and extracted five times with ether; the residue left on evaporation of the ether was treated with alcoholic oxalic acid, tetradehydroemetine hydrogen oxalate (8·95 g., 43%), m. p. 153—154°, crystallising immediately. The aqueous solution remaining after the ether-extraction was acidified with hydrochloric acid and evaporated to dryness, and the residue was extracted with acetone and alcohol. The extracts yielded, on evaporation and crystallisation from water, a further quantity of rubremetinium chloride (total, 8·28 g.; 46%).

The specific rotation of rubremetinium chloride was measured, for an air-dried sample containing 5·85% of water; the values are calculated for the anhydrous material: $[\alpha]_D^{15}$ +52·0°, $[\alpha]_{5461}^{15}$ +25·4° (*c*, 0·4 in water).

Hydrogenation of Rubremetinium Chloride.—A solution of the salt (4·0 g.) and sodium acetate trihydrate (3·5 g.) in ethanol (55 ml.) was shaken with hydrogen and platinic oxide (0·15 g.), rapid absorption of 1 mol. of hydrogen occurring. The filtered, pale yellow solution gave $[\alpha]_D^{17}$ −140° and on evaporation left a gum which was suspended in excess of sodium hydroxide solution and extracted with ether. The extracts, on evaporation and crystallisation from ethanol, gave a mass of pale yellow needles, m. p. 173—178° (3·5 g., 88%). On treatment with hot methanol (100 ml.) a portion of the material remained undissolved; it was collected and recrystallised several times from a larger volume of methanol, until the m. p. and rotation were constant. The resulting *complex*, containing one molecule each of α- and β-dihydrorubremetine and two molecules of methanol, formed fine colourless prisms, m. p. 127—128° (with sintering from 125°), $[\alpha]_D^{18}$ +21·2° (*c*, 0·176 in acetone) (Found: C, 71·1; H, 7·5. $2C_{29}H_{34}O_4N_2,2CH_3{\cdot}OH$ requires C, 71·2; H, 7·5%). The complex was decomposed by crystallisation several times from ethanol, the less soluble isomer, *β-dihydrorubremetine*, separating as very fine, feathery needles, m. p. 201—202°, $[\alpha]_D^{19}$ +406·3° (*c*, 0·148 in acetone) (Found: C, 73·5; H, 6·8; N, 6·1. $C_{29}H_{34}O_4N_2$ requires C, 73·4; H, 7·2; N, 5·9%).

The original methanol filtrate was concentrated to 50 ml. and, on its cooling, *α-dihydrorubremetine* crystallised; after repeated crystallisation from methanol it formed colourless needles, m. p. 197—198°, $[\alpha]_D^{15}$ −395° (*c*, 0·165 in acetone) (Found: C, 73·1; H, 7·4; N, 6·0%). Potentiometric titration (" Marconi " pH meter and glass electrode) of a solution of α-dihydrorubremetine in excess of aqueous-alcoholic hydrochloric acid against 0·1N-sodium hydroxide showed the substance to be a monoacidic base (Found: equiv., 457. Calc. for $C_{29}H_{34}O_4N_2$: equiv., 474).

Colour Reactions of the Dihydrorubremetines.—The two isomers gave identical results in the following reactions: (*a*) A bright carmine colour was imparted to a pine shaving moistened with hydrochloric acid and held in the vapour from the destructive distillation of dihydrorubremetine. (*b*) A trace of dihydrorubremetine, dissolved in ethanol, was treated with a drop of Ehrlich's *p*-dimethylaminobenzaldehyde reagent. An intense green colour was produced, which became red on addition of excess of reagent. (*c*) A solution of dihydrorubre-

metine in dilute acetic acid was treated with a solution of sodium diazobenzene-*p*-sulphonate. A brilliant red azo-dye was produced. Emetine hydrochloride and tetradehydroemetine hydrogen oxalate gave no colour under these conditions.

Mercuric Acetate Oxidation of the Dihydrorubremetines.—α-Dihydrorubremetine (0·1 g.), in dilute acetic acid (2 ml.), was treated with a solution of mercuric acetate (0·148 g.), potassium acetate (0·025 g.), and acetic acid (0·2 ml.) in water (3 ml.), and the mixture was heated under reflux at 110—120° (bath) for 3½ hours. When isolated in the usual manner, rubremetinium chloride (0·028 g., 21% calc. as hexahydrate) was obtained as scarlet needles, m. p. (air-dried) 126—127° (decomp.) both alone and in admixture with an authentic specimen of m. p. 121—123°. β-Dihydrorubremetine gave an identical yield of air-dried material, m. p. and mixed m. p. 123—125° (decomp.).

Attempted Oxidation of 3 : 4-*Dihydroisoquinolines with Mercuric Acetate.*—(With Dr. A. R. BATTERSBY.) 1-*n*-Butyl-3 : 4-dihydro*iso*quinoline (0·516 g.) was mixed with a solution of mercuric acetate (1·81 g.), potassium acetate (0·1 g.), and acetic acid (0·5 g.) in water (15 ml.) and heated under reflux for 7 hours. On cooling, there was a very slight deposit of mercurous acetate (90 mg.), which was removed. The filtrate was freed from mercury salts with hydrogen sulphide, and the resulting solution was made strongly alkaline with sodium hydroxide and extracted three times with ether, each ethereal extract being washed once with water. The combined extracts were dried and evaporated, to give a yellow oil (0·490 g.). A portion (0·22 g.) of this was converted into the picrate (0·44 g.), which formed yellow plates, m. p. 152—153°, undepressed on admixture with 1-*n*-butyl-3 : 4-dihydro*iso*quinoline picrate (m. p. 152—153°).

No reaction occurred when 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline (1 g.) was heated under reflux for 4 hours with a solution of mercuric acetate (3·5 g.) and acetic acid (1 ml.) in water (10 ml.).

Hydrogenation of Tetradehydroemetine.—A solution of tetradehydroemetine hydrogen oxalate (1·0 g.) in water (30 ml.) was shaken with hydrogen and platinic oxide (0·1 g.) at room temperature and pressure; 2·0 mols. of hydrogen were absorbed in 40 minutes. After removal of the catalyst, the solution was evaporated to dryness under reduced pressure. The residual yellow gum (0·95 g.) was dissolved in water and treated with hydrobromic acid (15 ml. of 2N.), but no emetine hydrobromide separated even after seeding. The base (0·72 g.) was recovered, dissolved in ether, mixed with benzoic anhydride (0·15 g.), and heated on the steam-bath for 45 minutes, the ether being allowed to evaporate. The product was worked up according to the directions of Pyman (*loc. cit.*), and benzoyl*iso*emetine (0·67 g., 78%) was obtained as white hexagonal prisms, m. p. 201—202°. One recrystallisation from acetone raised the m. p. to 202—203°; $[\alpha]_D^{17}$ was +48·0° (*c*, 2·0 in chloroform). Pyman gives m. p. 207—208° (corr.) and $[\alpha]_D$ +48·9°. No other reduction products could be isolated.

Tetradehydroemetine base (0·75 g.) (recovered from the hydrogen oxalate), dissolved in ethanol (40 ml.) and shaken with hydrogen and platinic oxide (0·1 g.), absorbed 2·0 mols. of hydrogen. On treatment of the product as described above, benzoyl*iso*emetine (0·146 g., 36%) was the sole crystalline material isolated.

Attempted Synthesis of 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*propenylisoquinoline* (XI).—2-(3 : 4-Dimethoxyphenyl)ethylamine (4·13 g.), dissolved in anhydrous ether (60 ml.), was treated dropwise with a solution of crotonyl chloride (1·3 g.) in anhydrous ether (40 ml.) with continuous shaking, a white precipitate being formed. After being left for several days, the mixture was treated with water (40 ml.), whereupon the precipitate dissolved and large yellow needles (1·74 g.) of the amide, m. p. 82—84°, separated from the aqueous phase. After the collection of this material, the aqueous layer was saturated with ammonium sulphate and the ethereal layer was separated. The aqueous layer was extracted thrice with ether, and the combined ethereal solutions on evaporation and crystallisation of the residue from water gave a further crop (1·1 g.; total, 98%) of crystalline amide, m. p. 84—85°. After recrystallisation twice from water the substance had m. p. 85—86°.

Phosphoric oxide (2·5 g.) was added to a solution of the foregoing amide (1 g.) in anhydrous toluene (20 ml.), and the mixture was refluxed for 10 minutes, the phosphoric oxide becoming yellow and sticky. A second portion of phosphoric oxide (2·5 g.) was then added and, after 15 minutes' refluxing, a third portion (2·0 g.); finally, the mixture was refluxed for 20 minutes, cooled, and treated cautiously with water (20 ml.), followed by hydrochloric acid (10 ml. of 2N.). After thorough shaking, the toluene layer was removed and extracted with two further portions of dilute hydrochloric acid, and the combined acid extracts were basified and extracted with ether. The ethereal extract, which became cloudy on exposure to air and darkened appreciably, was dried and evaporated, leaving the dihydro*iso*quinoline (XI) as a yellowish-

red gum (0·87 g., 94%) which would not crystallise. No crystalline hydrobromide, hydrogen oxalate, or picrate could be obtained. Solutions of the base or its salts darkened rapidly on exposure to air and light, forming resinous substances. Distillation of a sample of the base at 190° (bath)/2 × 10^{-5} mm. gave a dark brown, resinous distillate, and a large residue which polymerised to a hard black resin.

Diastereoisomeric Rubremetinium Salts.—Hot aqueous solutions of rubremetinium chloride (0·2 g. in 2 ml.) and sodium (+)- or (−)-camphor-10-sulphonate (0·88 g. in 1 ml.) were mixed; on cooling, the product crystallised in red leaflets (0·21 g., 92%) and was recrystallised from water (10 ml.). (+)-Rubremetinium (+)-camphor-10-sulphonate had m. p. 183—184° (decomp.); the (−)-camphor-10-sulphonate had m. p. 176—177° (decomp.). The two salts did not differ appreciably in solubility; they were readily soluble in ethanol and acetone, soluble in hot water, and almost insoluble in ethyl acetate.

The α-bromocamphor-π-sulphonates were prepared in a similar manner, with 0·1 g. of ammonium (+)- or (−)-α-bromocamphor-π-sulphonate; in each case the product formed orange-red leaflets (0·255 g., 100%). (+)-Rubremetinium (+)-bromocamphorsulphonate, crystallised from water (15 ml.), had m. p. 239° (sintering at 237°); it was noticeably less soluble than the (−)-bromocamphorsulphonate, which after crystallisation from water (10 ml.) had m. p. 217° (sintering at 213°). Both salts were readily soluble in ethanol and acetone and almost insoluble in ethyl acetate.

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United College, University of St. Andrews. [*Received, August 27th,* 1951.]

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77. *Reactions of Aromatic Nitro-compounds with Alkaline Sulphides. Part IV.* Disulphide Formation.*

By E. R. Ward and L. A. Day.

From a study of the reactions of *o*-dinitrobenzene with alkaline sulphides it is concluded that some diaryl disulphides may be formed from aromatic compounds containing labile nitro-groups by way of the aryl thiol or aryl thiophenoxide which is then oxidised by concurrently liberated nitrous acid or sodium nitrite. Alternative reaction mechanisms are discussed. The behaviour of 3 : 4- and 2 : 5-dinitrotoluenes with alkaline sulphides has been examined.

Hodgson and Ward (*J.*, 1949, **1316**) suggested that the formation of 2 : 2′-dinitrodiphenyl disulphide from *o*-dinitrobenzene by the action of sodium hydrogen sulphide was accounted for by the oxidation of the primary reaction product, *o*-nitrothiophenol, by concurrently liberated sodium nitrite. We now find this suggestion, with certain modifications, to be correct. These reactions constitute one possible general mode of formation of diaryl disulphides from aromatic compounds containing labile nitro-groups.

Pure sodium hydrogen sulphide in reaction with *o*-dinitrobenzene will liberate sodium nitrite and free nitrous acid (the latter unstable at the usual reaction temperatures). We have found that sodium nitrite or, more readily, free nitrous acid oxidises *o*-nitrothiophenol to 2 : 2′-dinitrodiphenyl disulphide. This reaction may proceed by way of the *S*-nitrosothiophenol, the formation of such compounds from thiophenols by nitrites, and their oxidation to the disulphides having been studied by Rheinboldt *et al.* (*Ber.*, 1926, **59**, 1311; 1927, **60**, 184; *J. pr. Chem.*, 1931, **130**, 133; B.P. 374 594). The intense colours formed during the reaction of alkaline sulphides with aromatic compounds containing labile nitro-groups support this idea, the colour of nitroso-thiols having been claimed as their most striking property (Lecher and Siefken, *Ber.*, 1926, **59**, 2594).

* Part III, *J.*, 1949, 1316.

Furthermore, disulphide formation from *o*-dinitrobenzene is almost completely suppressed by removal of nitrite ions from the reaction mixture, *e.g.*, by urea or ammonium salts, and it is largely suppressed by appreciable amounts of free alkali. Thus, whereas only the diaryl disulphide is formed by passing hydrogen sulphide into a solution of *o*-dinitrobenzene in hot methanol (whereby only nitrous acid is liberated), both the di- and the mono-sulphide are formed by sodium hydrogen sulphide; in the latter case reaction is due to both nitrous acid and the less reactive sodium nitrite, and is in competition with that between *o*-dinitrobenzene and *o*-nitrothiophenol which is favoured by the more alkaline medium. The effect of using varying molecular quantities of sodium hydrogen sulphide (Hodgson and Ward, *loc. cit.*) is thus accounted for.

An alternative possibility, that of direct sulphurisation of the 2 : 2′-dinitrodiphenyl sulphide by sodium hydrogen sulphide, has been found not to occur (cf. Fuson and Melamed, *J. Org. Chem.*, 1948, **13**, 690).

Parallel experiments with 3 : 4-dinitrotoluene were inconclusive. Sodium hydrogen sulphide gave a mixture, but sodium disulphide in boiling methanol produced only the disulphides (a mixture, owing to the lability of both nitro-groups), as was the case also with *o*-dinitrobenzene. It seems possible that in the disulphide reactions intermediate nitrothiophenoxides are not formed. However, 1 : 2-dinitronaphthalene and sodium disulphide give only the sulphide (and free sulphur), presumably by way of the thiol. That disulphides are formed by way of compounds of the type Ar·S·SH is not to be completely disregarded although the existence of such compounds is controversial. The same mixture of disulphides was obtained from 3 : 4-dinitrotoluene with sodium tetrasulphide, but under relatively strongly alkaline conditions some reduction to the isomeric nitrotoluidines also occurred. It is important that under none of our varied reaction conditions was 4-amino-3-nitrobenzaldehyde formed (cf. the analogous formation of *p*-aminobenzaldehyde from *p*-nitrotoluene; Hodgson and Beard, *J.*, 1944, 708).

Whilst one mode of formation of diaryl disulphides from aromatic polynitro-compounds by sodium hydrogen sulphide may be as suggested above, other mechanisms are also possible. One such we have already indicated for sodium disulphide, where there are complications caused by its ability to function in several ways (cf. Blanksma, *Rec. Trav. chim.*, 1901, **20**, 141), *e.g.*, by hydrolysis to sodium hydrogen sulphide and sodium hydroxide. This hydrolysis would account for the exclusive formation of diaryl monosulphides by this reagent in certain cases. It also must be borne in mind that according to Bullock and Forbes (*J. Amer. Chem. Soc.*, 1933, **55**, 232; cf. Raschevskaja, *J. Gen. Chem. Russia*, 1940, **10**, 1089), disulphide ions may arise in any reaction of aromatic nitro-compounds with any alkaline sulphide if reduction occurs simultaneously.

Blanksma (*Rec. Trav. chim.*, 1901, **20**, 121) failed to convert 2 : 2′-dinitrodiphenyl sulphide into the disulphide by sulphur in alcohol. Fuson and Melamed (*loc. cit.*) suggested that this could be accomplished by alkaline sulphides but they relied on an isolated observation that 4 : 4′-dinitrodiphenyl sulphide with sodium disulphide gave a mixture of the disulphide, *p*-nitrothiophenol, and *p*-aminothiophenol [cf. Lukashevich and Sergeeva, *Doklady Akad. Nauk. S.S.S.R.*, 1949, **67**, 1041 (*Chem. Abs.*, 1950, **44**, 1921); *Zhur. Obscheĭ Khim.*, 1949, **19**, 1493 (*Chem. Abs.*, 1950, **44**, 3456)].

There are moreover further complications, such as the reaction of nitrous acid or nitrites with the sulphides of sodium, or with sodium thiosulphate which may also be present when alkaline sulphides react with aromatic nitro-compounds. Much remains to be done to clarify alternative mechanisms of disulphide formation.

2 : 5-Dinitrotoluene with sodium hydrogen sulphide or sodium polysulphides yields 5-nitro-*o*-toluidine, 6-nitro-*m*-toluidine, and large amounts of unidentified amorphous material. There was no evidence of replacement of nitro-groups by arylthio-groups.

Experimental

Analyses are by Drs. Weiler and Strauss, Oxford.

Aqueous-methanolic sodium hydrogen sulphide was prepared by Hodgson and Ward's method (*J.*, 1948, 242). All the experiments were carried out under reflux, a rapid stream of nitrogen serving to exclude air and to provide efficient agitation.

Reaction of o-Nitrothiophenol with Sodium Nitrite.—*o*-Nitrothiophenol (1 g.) in ethanol (10 c.c.) was allowed to react with sodium nitrite (0·1 g.) for 15 minutes. After cooling, 2 : 2′-dinitrodiphenyl disulphide (0·65 g., 65%), m. p. 194—196° (Hodgson and Ward, *loc. cit.*, give 196—198°), was precipitated. Oxidation of the filtrate with potassium ferricyanide gave a yellow product (0·35 g.), m. p. 95—112°.

Reaction of o-Nitrothiophenol with Nitrous Acid.—The above experiment, with the addition of one equivalent of sodium hydrogen sulphate to liberate nitrous acid, gave 2 : 2′-dinitrodiphenyl disulphide (0·9 g., 91%), m. p. 192—195°. The filtrate on oxidation gave 0·05 g. of material, m. p. 98—113°.

Experiments with 2 : 2′-Dinitrodiphenyl Disulphide.—This was recovered unchanged after being boiled with aqueous sodium nitrite for 15 minutes and was only slightly affected by boiling aqueous sodium hydrogen sulphide (*ca.* 1 mol.) during 15 minutes.

Reactions of o-Dinitrobenzene.—(*a*) *o*-Dinitrobenzene (2 g.) in methanol (20 c.c.) was treated with a rapid stream of hydrogen sulphide during 25 minutes. The solution slowly darkened and a precipitate was formed. After cooling, the latter was removed, washed with water, and dried (0·8 g.). After extraction with cold carbon disulphide it afforded crude 2 : 2′-dinitrodiphenyl disulphide, m. p. 194° (from acetone), not depressed on admixture with an authentic specimen.

(*b*) *o*-Dinitrobenzene (2 g.) and urea (1 g.) in methanol (20 c.c.) were treated with sodium hydrogen sulphide (15 c.c.; *ca.* 0·75 mol.) during 5 minutes and the whole was heated for a further 10 minutes. After cooling, the solid product was collected, washed with a little cold methanol, dried, and extracted with cold carbon disulphide, affording crude 2 : 2′-dinitrodiphenyl sulphide, m. p. 94—99° (Found : S, 11·6. Calc. for $C_{12}H_8O_4N_2S$: S, 11·6%). Similar results were obtained with ammonium acetate in place of urea.

(*c*) *o*-Dinitrobenzene (2 g.) in methanol (20 c.c.) was treated with aqueous sodium sulphide (0·75 g., 0·8 mol.; 5 c.c.) as in (*b*). The sole product was pure monosulphide (0·8 g.), m. p. 119—122°.

(*d*) The previous experiment was repeated with the addition of sodium hydrogen carbonate (0·5 g.) and treatment with sodium hydrogen sulphide (1 mol.). The product was almost pure monosulphide (1·5 g.), m. p. 116—121° (Found : S, 11·3. Calc. for $C_{12}H_8O_4N_2S$: S, 11·6%).

Reactions of 3 : 4-Dinitrotoluene.—(*a*) 3 : 4-Dinitrotoluene was unaffected when a rapid stream of hydrogen sulphide was passed into a solution of it in boiling methanol.

(*b*) 3 : 4-Dinitrotoluene (2 g.) in methanol 20 c.c.) was treated with sodium hydrogen sulphide (30 c.c.; 1·5 mols.) for 5 minutes and the whole heated for a further 10 minutes. Cooling and acidification by dilute hydrochloric acid afforded an oil which solidified (1·4 g.). This was extracted by cold carbon disulphide and recrystallised from acetone, giving light yellow needles, m. p. 145—153° (Found : S, 16·2. Calc. for $C_{14}H_{12}O_4N_2S$: S, 10·5. Calc. for $C_{14}H_{12}O_4N_2S_2$: S, 19·0%). The acetone mother-liquors on evaporation to dryness gave a dark red product of low m. p. which could not be crystallised.

(*c*) The foregoing experiment was repeated with the addition of urea (1·0 g.). The main yellow product could not be obtained in a satisfactory crystalline form and appeared to contain sulphur.

(*d*) 3 : 4-Dinitrotoluene (2 g.) in ethanol (12 c.c.) was treated with aqueous sodium tetrasulphide (12 c.c., 0·33 mol.) containing sodium hydroxide (0·75 g.) (cf. Hodgson and Beard, *loc. cit.*) for 45 minutes and steam was then passed into the mixture. The orange-coloured distillate, collected after removal of alcohol, afforded by ether-extraction mixed nitrotoluidines (0·2 g.). After purification these had m. p. 77—78° (Found : N, 18·3. Calc. for $C_7H_8O_2N_2$: N, 18·4%). The residue in the flask consisted of tar and a red water-soluble compound which could not be identified. Reactions with sodium disulphide or tetrasulphide in methanol without the addition of alkali afforded, apparently, mixtures of disulphides containing small amounts of free sulphur.

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78. *Synthesis of Carbohydrates by Use of Acetylenic Precursors. Part II.* Addition Reactions of* cis- *and* trans-*But-2-ene-1 : 4-diol Diacetates. Synthesis of* DL-*Erythrulose.*

By R. A. Raphael.

The reactions of the above two diacetates with per-acids, osmium tetroxide-catalysed hydrogen peroxide, hypobromous acid, and bromine have been carried out. The stereochemistry of the conversion of the adducts into tetritol tetra-acetates has been investigated and interpreted. DL-Erythrulose has been obtained from the hypobromous acid adducts.

The acetylenic approach to the synthesis of carbohydrates frequently leads to compounds containing an ethylenic double bond flanked by carbon atoms each attached to an acetoxyl group. It was of obvious interest, therefore, to examine the stereochemical effect, if any, exercised by the acetoxyl groups on addition to the double bond and on the subsequent substitution of the added groups. The simplest representatives, *cis*- and *trans*-but-2-ene-1 : 4-diol diacetates, $AcO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OAc$ (I), were chosen for study; both possible end products, erythritol and DL-threitol, are well-characterised compounds.

The *trans*-diacetate (I) was prepared by interaction of *trans*-1 : 4-dibromobut-2-ene and potassium acetate in glacial acetic acid, and the *cis*-isomer by partial catalytic hydrogenation of but-2-yne-1 : 4-diol diacetate. From the latter reaction a small quantity of crystalline by-product was obtained which proved to be a dimer of the main product; as it appeared to be saturated it may be formulated as one of the stereoisomers of 1 : 2 : 3 : 4-tetrakisacetoxymethyl *cyclo*butane. Such dimerisation of ethylenic derivatives is well known to occur under the influence of light (*e.g.*, the formation of truxillic and truxinic acids) or heat (Dykstra, *J. Amer. Chem. Soc.*, 1934, **56**, 1625; Cupery and Carothers, *ibid.*, p. 1167) but formation of a *cyclo*butane ring during catalytic hydrogenation is new. An alternative constitution based on dimerisation to the acyclic

$$AcO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_2{\cdot}OAc){\cdot}C(CH_2{\cdot}OAc){:}CH{\cdot}CH_2{\cdot}OAc$$

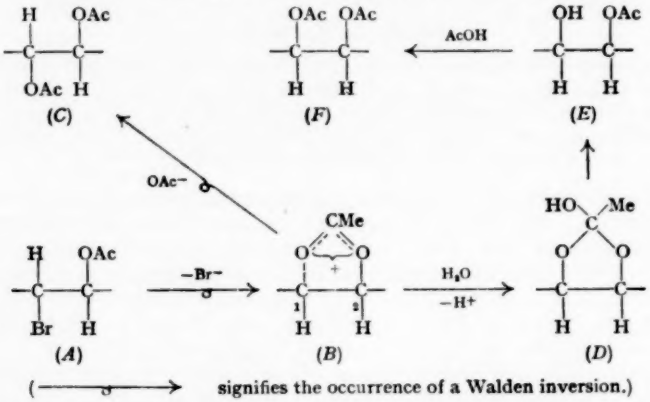
(cf. Bergmann, *Trans. Faraday Soc.*, 1939, **35**, 1025) and subsequent hydrogenation to the saturated compound is considered less likely.

The action of peracetic acid on the *trans*-diacetate (I) gave, after complete acetylation of the product, erythritol tetra-acetate; similar treatment of the *cis*-compound produced threitol tetra-acetate. Osmium tetroxide-catalysed *cis*-hydroxylation of the *cis*-diacetate with a *tert.*-butanol solution of hydrogen peroxide furnished crystalline erythritol 1 : 4-diacetate which gave erythritol tetra-acetate on complete acetylation. Under these conditions the *trans*-diacetate gave a liquid glycol converted on acetylation into threitol tetra-acetate. All these results are in full accord with stereochemical theory (see Part I).

trans-Addition of hypobromous acid to the *cis*- and *trans*-compounds (I) was smoothly effected by aqueous *N*-bromosuccinimide (Part I), to give homogeneous liquid bromohydrins which in view of the above precedents of "normal" addition were assigned the configurations *threo*- (II) and *erythro*-2-bromobutane-1 : 3 : 4-triol 1 : 4-diacetate respectively. The conversion of these compounds into tetritol tetra-acetates is of considerable stereochemical interest in view of the recent work of Winstein and his collaborators on the effect of vicinal substituents on the replacement of a bromine atom (for full references see Braude, *Ann. Reports*, 1949, **46**, 122). The relevant conclusions of the American workers may be briefly summarised with reference to the *threo*-bromo-acetate (*A*). Reaction with silver or potassium acetate results firstly in the removal of bromide ion with accompanying Walden inversion to give the cyclic acetoxonium ion (*B*). The subsequent reactions depend on the nature of the solvent. In dry acetic acid, (*B*) is attacked by acetate ion at the back of $C_{(1)}$ or $C_{(2)}$ (the examples studied gave symmetrical structures), with a second inversion that produces the *threo*-diacetate (*C*); thus there is overall retention of configuration. In moist acetic acid or ethanol, however, the predominating reaction is the attack of a water molecule with the expulsion of a proton, to give the unstable orthomonoacetate (*D*) the

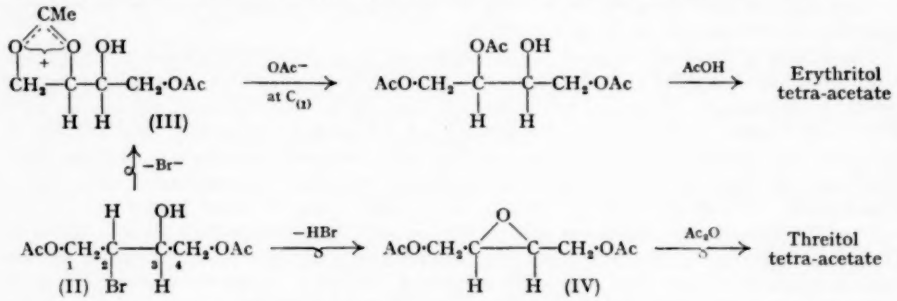
* Part I, *J.*, 1949, S 45.

ring of which then opens to yield the monoacetate (*E*), esterification furnishing finally the diacetate (*F*). Since none of these reactions involves a Walden inversion the diacetate (*F*) possesses the *erythro*-configuration, *i.e.*, overall inversion of configuration occurs. Analogous steric considerations apply to the *erythro*-isomer of (*A*).



The bromohydrins (II) represent more complex examples of this type of replacement since removal of bromide ion in this case allows of two possibilities, namely, the formation of an acetoxonium ring involving $C_{(1)}$ and $C_{(2)}$ or the formation of an epoxide between $C_{(2)}$ and $C_{(3)}$. The practical results of the replacement reactions were as follows.

Treatment of the *erythro*-bromohydrin with potassium acetate in dry acetic acid gave exclusively threitol tetra-acetate; the same reagent in moist ethanol gave, after treatment with acetic anhydride, erythritol tetra-acetate only. Similar reactions involving the *threo*-bromohydrin (II) gave mainly erythritol tetra-acetate in dry acetic acid and threitol tetra-acetate in moist alcohol, although in this case the specificity was less clear-cut.



These results may be interpreted by the mechanism illustrated above for the case of the *threo*-bromohydrin (II); it seems to be the only explanation capable of fully so doing. Abstraction of the bromide ion by potassium acetate in dry acetic acid results in the formation of the cyclic acetoxonium ion (III) with inversion of configuration at $C_{(2)}$. Attack of acetate ion then takes place at the non-asymmetric $C_{(1)}$ which is considerably easier of access than the more sterically hindered $C_{(2)}$; overall inversion of configuration has thus occurred to give, after esterification, erythritol tetra-acetate. Reaction in moist alcohol, however, gives rise to the formation, with Walden inversion, of the epoxide (IV) which, on treatment with acetic anhydride, undergoes ring opening, again with Walden inversion, to threitol tetra-acetate; the overall effect is that of retention of configuration (for detailed mechanism of epoxide formation and fission see Winstein and Lucas, *J. Amer. Chem. Soc.*, 1939, **61**, 1576). In order to confirm the second mechanism an attempt was made to isolate the epoxide (IV). The oily product, however, proved to be inhomogeneous,

although it gave threitol tetra-acetate in high yield on acetylation; it was possibly a mixture of the required epoxide (IV) with threitol 1 : 2 : 4-triacetate, the latter being formed by interaction of (IV) with the acetic acid formed in the reaction. Exactly analogous arguments account for the results derived from the *erythro*-bromohydrin.

The addition of bromine to the *trans*-diacetate (I) has already been recorded by Griner (*Bull. Soc. chim.*, 1893, **9**, 219) and, in agreement with his results, the reaction gave the crystalline *erythro*-2 : 3-dibromobutane-1 : 4-diol diacetate (V). This compound gave the *same* product, erythritol tetra-acetate, on treatment with potassium acetate in either dry or moist acetic acid. This result may be readily interpreted on the basis of formation of a symmetrical dicyclic bisacetoxonium ion (VI) whence attack by either two acetate ions or two water molecules would give the same compound.

Bromination of the *cis*-diacetate (I) gave a liquid dibromide which, after distillation, largely solidified. The solid component proved to be the *erythro*-dibromide (V) while redistillation of the liquid again gave a distillate which partly solidified. From this it would seem that the expected *threo*-dibromide underwent thermal isomerisation to the *erythro*-isomer during distillation. Models show that in the stable, uniplanar, zig-zag *d* constellation of the four " backbone " carbon atoms (cf. Prelog, *J.*, 1950, 424) the two bromine atoms in the *erythro*-isomer are widely separated, whereas in the *threo*-dibromide there is strong steric interference.

Chromium trioxide oxidation of either the *erythro*- or the *threo*-bromohydrin (II) gave the same ketone, 2-bromo-1 : 4-diacetoxybutan-3-one which, by treatment with silver acetate in acetic acid, yielded DL-erythrulose triacetate. Hydrolysis with baryta then gave DL-erythrulose, characterised as its phenylosazone.

Experimental

trans-*But-2-ene*-1 : 4-*diol Diacetate* (I).—*trans*-1 : 4-Dibromobut-2-ene was heated with a solution of potassium acetate in glacial acetic acid according to the directions of Prevost (*Compt. rend.*, 1926, **183**, 1292). A solid bromine-containing impurity co-distilling with the main fraction was found to be 1 : 2 : 3 : 4-tetrabromobutane, m. p. 116—117°; for complete removal of this an alcoholic solution of the product had to be heated under reflux for 6 hours with zinc wool. The pure *trans*-diacetate had b. p. 120—121°/16 mm., m. p. 13—14°, n_D^{21} 1·4447.

cis-*But-2-ene*-1 : 4-*diol Diacetate* (I).—But-2-yne-1 : 4-diol diacetate was prepared from the glycol by acetic anhydride (Johnson, *J.*, 1946, 1009); it solidified to prismatic crystals, m.p. 27—29° (Found : C, 56·1; H, 5·8. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%). A solution of it (34 g.) in ethyl acetate (50 c.c.) was shaken under hydrogen with palladium–calcium carbonate (10%; 1 g.) until 1 mol. of hydrogen had been absorbed (4911 c.c. at 20°/754 mm.). Removal of catalyst and solvent and distillation gave the cis-*diacetate* (28 g.), b. p. 120—121°/18 mm., n_D^{19} 1·4435 (Found : C, 55·9; H, 7·2. $C_8H_{12}O_4$ requires C, 55·85; H, 7·05%).

The distillation residue solidified on cooling and was extracted with boiling ethanol. The extract on cooling deposited the *dimer* (1·2 g.) as stout needles, m. p. 104—105° [Found : C, 55·75; H, 6·7. *M* (ebullioscopic in acetone), 363. $(C_8H_{12}O_4)_2$ requires C, 55·85; H, 7·05%; *M*, 344]. Hydrolysis with a catalytic quantity of sodium methoxide furnished the parent glycol as a thick oil, Schotten–Baumann benzoylation of which gave the corresponding *benzoate* crystallising in needles, m. p. 149—150°, from *n*-butanol [Found : C, 72·85; H, 5·55. $(C_{18}H_{16}O_4)_2$ requires C, 72·95; H, 5·45%].

Action of Peracetic Acid on (I).—A solution of hydrogen peroxide (30%; 19 g.) in glacial acetic acid (25 c.c.) was heated to 85° for 1 hour and then cooled to 25° (Scanlan and Swern, *J. Amer. Chem. Soc.*, 1940, **62**, 2305). To this solution was added the *trans*-diacetate (I) (4·3 g.); as no exothermic reaction was observed the mixture was warmed to 50° and kept at this temperature for 16 hours. Evaporation under reduced pressure gave a viscous oil which was heated under reflux with acetic anhydride (10 c.c.) for 3 hours. The excess of anhydride was removed under reduced pressure, the residue treated with water, and the precipitated oil

extracted with ether. Washing with sodium hydrogen carbonate solution, drying ($MgSO_4$), and evaporation of the ether gave an oil which rapidly solidified; crystallisation from benzene–light petroleum (b. p. 60—80°) gave erythritol tetra-acetate (3·7 g., 51%) as prismatic needles, m. p. 89—90°, undepressed on admixture with an authentic specimen. The yield of product was found to be much improved (5·7 g., 79%) and the time of reaction considerably shortened if performic acid (18 c.c. of 98% formic acid and 7 g. of 30% H_2O_2) were used (Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786). The resulting reaction mixture was distilled in steam to hydrolyse the formoxy-group, and the residue left after evaporation to dryness was acetylated as above.

When the *cis*-diacetate (I) (4·3 g.) was treated with peracetic acid as described above, the only product consisted of DL-threitol tetra-acetate (4·1 g., 57%), crystallising in large prisms, m. p. 54—55°, after slow crystallisation from benzene–light petroleum (b. p. 60—80°) with preliminary seeding (Griner, *Compt. rend.*, 1893, **117**, 555 gives m. p. 53°). A small quantity of the product was catalytically deacetylated with sodium methoxide in methanol, and the residue after evaporation treated with concentrated hydrochloric acid and benzaldehyde; the resulting dibenzylidene compound crystallised in needles, m. p. 222°, from a large volume of ethanol (Maquenne and Bertrand, *Compt. rend.*, 1901, **132**, 1566, give m. p. 220° for dibenzylidene DL-threitol).

Action of Milas's Reagent on (I).—To a solution of hydrogen peroxide in *tert.*-butanol (6%; 20 c c.) was added the *trans*-diacetate (I) (4·3 g.), followed by a *tert.*-butanol solution of osmium tetroxide (1%; 1 c.c.). After 36 hours at room temperature the reaction mixture was evaporated under reduced pressure, to give a viscous oil which was acetylated by heating it with acetic anhydride (15 c.c.). Isolation and crystallisation as described above gave threitol tetra-acetate (5·3 g., 73%), m. p. and mixed m. p. 54—55°.

Treatment of the *cis*-diacetate (I) (4·3 g.) with the same reagent gave a viscous oil which rapidly solidified. Crystallisation from benzene gave *erythritol* 1 : 4-*diacetate* (3·9 g., 76%) as needles, m. p. 93—94° (Found: C, 46·3; H, 7·1. $C_8H_{14}O_8$ requires C, 46·6; H, 6·85%). This compound is possibly identical with the erythritol diacetate of unknown constitution, m. p. 89—91°, obtained by Fischer and Rund (*Ber.*, 1916, **49**, 98). Treatment of the product with acetic anhydride gave an almost quantitative yield of erythritol tetra-acetate, m. p. and mixed m. p. 89—90°.

threo- (II) *and* erythro-2-*Bromobutane*-1 : 3 : 4-*triol* 1 : 4-*Diacetate*.—A mixture of the *cis*-diacetate (I) (26 g.), powdered freshly crystallised *N*-bromosuccinimide (30 g.), water (50 c.c.), and acetic acid (0·2 c.c.) was shaken at room temperature for 16 hours. Water and ether were then added, and the ethereal layer was washed with sodium hydrogen carbonate solution and water and finally dried ($MgSO_4$). Evaporation and distillation gave threo-3-*bromobutane*-1 : 2 : 4-*triol* 1 : 4-*diacetate* (II) (33·6 g., 83%), b. p. 138—140°/2 × 10^{-2} mm., n_D^{15} 1·4796 (Found: C, 35·5; H, 5·0. $C_8H_{13}O_5Br$ requires C, 35·7; H, 4·9%).

Similarly the *trans*-diacetate (I) (17·2 g.) gave the erythro-*bromohydrin* (19·8 g., 74%), b. p. 130—132°/3 × 10^{-2} mm., n_D^{18} 1·4810 (Found: C, 35·55; H, 4·9%).

Action of Potassium Acetate on the Bromohydrins.—(a) *In dry acetic acid* (glacial acetic acid boiled for 1 hour with 5% of acetic anhydride). A mixture of the *erythro*-bromohydrin (1·7 g.), anhydrous potassium acetate (2 g.), and dry acetic acid (15 c.c.) was heated under reflux for 16 hours. The solvent was evaporated under reduced pressure, and water and ether were added to the residue. The ethereal layer was washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$); evaporation gave an oil which solidified. Slow crystallisation from benzene–light petroleum (b. p. 60—80°) gave threitol tetra-acetate (1·52 g., 83%), m. p. and mixed m. p. 53—54°.

Similarly the *threo*-bromohydrin (II) (2·1 g.) was treated with potassium acetate (2·5 g.) and dry acetic acid (25 c.c.); working up as above gave an oil which slowly solidified (2·1 g.). The product was dissolved in a small quantity of benzene (*ca.* 5 c.c.), and light petroleum (b. p. 60—80°) added slowly until a slight permanent turbidity was obtained. The solution was then seeded with a crystal of erythritol tetra-acetate and kept at room temperature for 24 hours. The precipitated crystalline mass (1·2 g.) had m. p. 85—87° undepressed on admixture with erythritol tetra-acetate. The mother-liquors were evaporated to dryness, the residue was dissolved in the minimum quantity of benzene, and the solution again treated to turbidity with light petroleum (b. p. 60—80°). The turbidity was removed with a drop of benzene, a seed of threitol tetra-acetate was introduced, and the solution cooled slowly to 0°, at which it was kept for 36 hours. The crystals thus obtained (0·24 g.) consisted of threitol tetra-acetate, m. p. and mixed m. p. 54—55°.

(b) *In moist alcohol* (95%). The *erythro*-bromohydrin (2·3 g.), potassium acetate (2·6 g.), and moist alcohol (25 c.c.) were heated under reflux for 16 hours. The solvent was removed under reduced pressure, leaving a residue smelling strongly of acetic acid; to this was added acetic anhydride (10 c.c.), and the mixture heated under reflux for 4 hours. Working up as already described gave erythritol tetra-acetate (1·8 g., 73%), m. p. and mixed m. p. 88—89°.

Similarly the *threo*-bromohydrin (II) (3·1 g.), potassium acetate (3·5 g.), and moist alcohol (30 c.c.) gave, after acetylation, a product (2·9 g.) from which threitol tetra-acetate (1·9 g.) and erythritol tetra-acetate (0·3 g.) were isolated. In one experiment the residue left after evaporation was treated with water and ether instead of acetic anhydride, in an attempt to isolate the intermediate epoxide. Evaporation of the washed and dried ethereal solution gave an oil which boiled continuously in the range 80—120°/5 × 10^{-3} mm.

Action of Bromine on (I).—To a solution of the *trans*-diacetate (I) (10 g.) in carbon tetrachloride (75 c.c.) was slowly added at room temperature a solution of bromine (9·1 g.) in carbon tetrachloride (25 c.c.). Evaporation of the solvent gave a crystalline mass which was crystallised from light petroleum (b. p. 60—80°) to give an almost quantitative yield of the *erythro*-dibromide (V), prisms, m. p. 87—88° (Griner, *loc. cit.*, gives m. p. 87°).

Similarly the *cis*-diacetate (I) (4·8 g.) in carbon tetrachloride (10 c.c.) was treated with a solution of bromine (5 g.) in carbon tetrachloride (15 c.c.). Evaporation gave an oil which was distilled at 102—104°/6 × 10^{-4} mm., n_D^{17} 1·5020. The distillate largely solidified; the liquid expressed from the solid was again distilled but again the distillate partly solidified. The solid products crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 87—88°, undepressed on admixture with the *erythro*-dibromide (V).

Action of Potassium Acetate on the erythro-*Dibromide* (V).—The dibromide (3·3 g.) was heated under reflux with dry acetic acid (25 c.c.) and potassium acetate (5 g.) for 16 hours. Working up by the usual procedure gave erythritol tetra-acetate (2·6 g., 66%), m. p. and mixed m. p. 86—88°.

When similar quantities of reactants were heated in moist (95%) acetic acid a similar yield of erythritol tetra-acetate was obtained.

DL-*Erythrulose.*—The *erythro*-bromohydrin (15 g.) was dissolved in acetic acid (15 c.c.), and a solution of chromium trioxide (8 g.) in acetic acid (95%; 50 c.c.) added slowly with cooling and shaking. The solution was kept for 16 hours at room temperature and the acetic acid then evaporated at 25°/0·1 mm. Water was added to the residue, and the precipitated oil isolated by means of ether. Distillation gave 1 : 4-*diacetoxy*-2-*bromobutan*-3-*one* (10·1 g.), b. p. 100—102°/10^{-4} mm., n_D^{17} 1·4795. A similar yield of the identical product was obtained from the *threo*-bromohydrin (II) (Found: C, 35·8; H, 4·35. $C_8H_{11}O_5Br$ requires C, 36·0; H, 4·15%).

The bromo-ketone (5·6 g.), silver acetate (6 g.), and glacial acetic acid (50 c.c.) were heated under reflux for 6 hours. The cooled reaction mixture was filtered and the solids washed with a little acetic acid. The combined filtrates were reheated with a further quantity of silver acetate (6 g.) for 3 hours longer. The cooled solution was filtered and the filtrate evaporated under reduced pressure. The residual oil was dissolved in ether, and the solution filtered, evaporated, and distilled.

DL-*Erythrulose triacetate* was obtained as a pale yellow oil (3·3 g.), b. p. 108—110°/10^{-4} mm., n_D^{18} 1·4545 (Found: C, 48·25; H, 5·7. $C_{10}H_{14}O_7$ requires C, 48·75; H, 5·75%).

To an ice-cold filtered solution of barium hydroxide octahydrate (8 g.) in water (80 c.c.) was added the ketose triacetate (2·5 g.), and the mixture kept at 0° with occasional shaking for 90 minutes (cf. Wolfrom, Brown, and Evans, *J. Amer. Chem. Soc.*, 1943, **65**, 1026). The solution was saturated with carbon dioxide, and the resulting barium carbonate filtered off. Dilute sulphuric acid (4N.) was then carefully added until a slight excess was present. The barium sulphate was centrifuged off, and the solution evaporated under reduced pressure to one-quarter of its bulk. This solution was then passed through a column of " Bio-Deminrolit," and the effluent evaporated to dryness under reduced pressure. DL-Erythrulose was obtained as a viscous syrup (0·8 g.) which did not solidify; it was dissolved in a small quantity of water and heated with an excess of a solution of phenylhydrazine in 50% acetic acid. The precipitated brown solid was filtered off, dried on porous tile, and purified by crystallisation from benzene, from which the DL-erythrulose phenylosazone separated in yellowish-brown needles, m. p. 166—168° (Fenton and Jackson, *J.*, 1899, **75**, 8, record m. p. 167° for erythrosazone obtained from the ferrous–peroxide oxidation of erythritol) (Found: N, 18·4. Calc. for $C_{16}H_{18}O_2N_4$: N, 18·8%).

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79. *Solutions of Alcohols in Non-polar Solvents. Part II.* Volume Relations in Dilute Solutions of Primary Alcohols in Benzene, Heptane, and* cyclo*Hexane.*

By L. A. K. Staveley and (Miss) Betty Spice.

An apparatus is described for the accurate determination of the small volume changes which occur when one liquid is mixed with a much larger quantity of another. Measurements have been made at 20° of the volume changes occurring when the first six primary alcohols, and *n*-octanol and *n*-decanol, are mixed with benzene, heptane, and *cyclo*hexane, to give solutions in which the mole-fraction, x, of the alcohol is between 0·005 and 0·035. For the benzene solutions, the volume increase v per mole of alcohol is an almost linear function of x. In the other two solvents, the v–x plots are curved, their shapes being consistent with the view, based on spectroscopic work, that in the concentration range concerned the alcohols associate to trimers. In benzene, however, it is possible that association starts by the production of even larger aggregates, perhaps tetramers.

By extrapolation, values of the partial molar volumes at infinite dilution ($\bar{V}_\infty$) of the alcohols in the three solvents have been derived. Whereas in heptane, $\bar{V}_\infty$ increases by almost constant increments on passing from one alcohol to the next (from ethanol to decanol), this is not so in benzene and *cyclo*hexane, where the increments show an alternation. The observed effects are compared with those which would be expected if, from pentanol onwards, the monomeric alcohol molecules tend to coil into a cyclic configuration. The results are not inconsistent with this possibility, but do not definitely prove it.

In Part I * of this series it was suggested on the basis of solubility studies that, in dilute benzene solutions of the normal primary alcohols, the interaction between the hydroxyl group and the surrounding benzene molecules underwent a change when the hydrocarbon group of the alcohol molecule became sufficiently long to be capable of screening the hydroxyl group. The evidence indicated that this change took place on passing from butanol to pentanol, and it was tentatively proposed that the monomeric molecules of pentanol and higher alcohols, unlike those of their predecessors, had a tendency to adopt a coiled configuration in benzene solution, this tendency being perhaps encouraged by the cyclic character of the solvent molecules. Since the spatial requirements of a flexible molecule in such an environment might differ according to whether it was coiled or extended, it seemed worth while to examine the partial molar volumes at infinite dilution of alcohols of increasing chain length. The partial molar volumes at infinite dilution can be found by extrapolation either from density determinations on progressively more dilute solutions, or from measurements of the volume changes which occur when dilute solutions are made by mixing appropriate amounts of the alcohol and solvent. Numerous values of the densities of dilute solutions of alcohols in non-polar solvents have been published (mostly in connection with dipole moment measurements), but with the possible exception of those of Harms (*Z. physikal. Chem.*, 1943, **53**, *B*, 280) they are far too inaccurate to be of any use for the present purpose, and even Harms's results scarcely extend to sufficiently low concentrations. Association of alcohol molecules in non-polar solvents becomes appreciable at such low concentrations that the measurements must be made on very dilute solutions if extrapolation is to have any value and then, to achieve the accuracy sought, very precise density determinations are essential. In a benzene solution containing ethyl alcohol at a mole-fraction of 0·01, an error in the density of 1 : 80,000 would involve an error of approximately 0·1 c.c. in the apparent molar volume of the solute. We have accordingly preferred to measure the volume change on mixing of alcohol and solvent, since this is virtually a direct measurement of the difference between the volume of a given mass of the pure alcohol and its effective volume in the dilute solution.

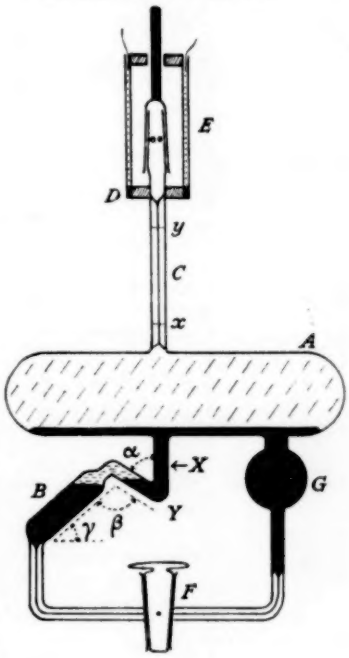
* Part I, *J.*, 1951, 2516.

Whereas, as stated in Part I, attempts to determine the solubility in non-polar solvents other than benzene were not successful, no such limitation applies to the study of volume changes on mixing. With a view to studying the influence which the shape of the solvent molecules may have on the configuration adopted by flexible solute molecules, we have used benzene, *n*-heptane, and *cyclo*hexane as solvents. The alcohols examined were those from methanol to *n*-hexanol inclusive, *n*-octanol and *n*-decanol.

Experimental

In the experiments with any one alcohol in any one solvent, the mole fraction of the alcohol was usually between 0·005 and 0·035. Keyes and Hildebrand (*J. Amer. Chem. Soc.*, 1917, **39**, 2126) have described an apparatus for measuring volume changes on mixing liquids. Preliminary experiments showed that, while this apparatus serves admirably if the quantities of the two liquids are not very different, it is not suitable when one of them is very much larger than the other as in our work, for it becomes necessary to construct the container for the solute from capillary or semi-capillary tubing, and the operation of mixing is then excessively difficult. The apparatus shown in Fig. 1 was therefore devised. The capillary *C* was approximately 7 cm. long, and was provided with reference marks, *x* and *y*. The cross-section between *x* and *y* had been carefully determined, and was approximately 2×10^{-2} sq. cm. The total internal volume up to one of the marks on the capillary, determined by filling the vessel with water and weighing it, was ~110 c.c. The capacity of the barrel *A* was about 85 c.c. and that of the bulb *B* about 7 c.c. The angles α, β, and γ were 60°, 105°, and 45° respectively. The apparatus was held securely in a metal frame so that it could be rocked (in the plane of the paper) about an axis through the point *X*. It was immersed in a thermostat to just above the base of the jacket *E*. This jacket was electrically heated so that the temperature inside it was held constant a few degrees above the thermostat temperature (20°), thus eliminating the possibility of any vapour condensing from the meniscus in the capillary into the space above it. The ground glass cap above the capillary was greased with a lubricant made from dextrin, mannitol, and glycerol.

Fig. 1. *Apparatus for determining volume changes on mixing, shown containing the alcohol, hydrocarbon, and mercury before mixing.*



The vessel was filled as follows. Into the weighed empty vessel was introduced sufficient mercury to fill completely the lower part of the vessel with an overflow of several c.c. into the barrel *A*, and the vessel was then weighed again. Care had to be taken to see that no air bubbles were trapped by the mercury (they could easily be removed by rocking the vessel). The tap *F* was closed, and the vessel turned clockwise through about 60° and clamped. The alcohol was then introduced from a pipette provided with a tap and a long thin metal capillary with a very small opening. This capillary was inserted into the vessel until its tip reached the point *Y*, and the required quantity of alcohol forced into the bulb by applying pressure to the pipette. This operation could be conducted without introducing any air bubbles, but degassed alcohol was used so that any small bubbles admitted into *B* would dissolve. The weight of the alcohol trapped in the bulb *B* was found from the change in weight of the pipette. The vessel was now clamped in its frame in a vertical position, the cone greased, and the jacket *E* fitted on the rubber collar *D*. The vessel was placed in the thermostat and a suitable current passed through the heating coil *E*. The solvent, previously degassed, was then blown into the barrel *A* through a metal capillary, until finally its meniscus was just above the reference mark *x*. Dry air was blown into the capillary above the meniscus to ensure that the glass walls of the upper part of the vessel would be free from any drops of adhering solvent, and the vessel was then closed with the ground-glass cap. When temperature equilibrium had been

attained, the position of the meniscus relative to one of the reference marks x and y was read with a travelling microscope. Before every reading, the ground-glass cap was turned to be open momentarily to the atmosphere. The volume of solvent in the apparatus was found by subtracting the volume of alcohol and mercury from the total volume of the vessel.

For mixing of the liquids, the vessel was tilted anticlockwise through 45° and the tap F opened, whereupon the alcohol was displaced by mercury into the barrel. (The function of the bulb G was to ensure that in this operation the head of mercury would not fall to such an extent that expulsion of the alcohol from B would be incomplete.) In order to wash out the bulb B, the vessel was tilted until it was inclined at 45° to the right, whereupon the solution entered B.

TABLE 1. *Volume Changes.*

(v is the volume increase in c.c. occurring on mixing of one mole of alcohol with sufficient solvent to give a solution in which the mole-fraction of the alcohol is x.)

Alcohol	Solvent								
Methanol	Benzene	v	0·76	0·73	0·77	0·68			
		10^3x	9·0	16·4	22·1	27·6			
	Heptane	v	6·83	5·41	5·33	3·85			
		10^3x	4·8	10·8	14·3	27·3			
	*cyclo*Hexane	v	3·31	3·17	2·81	2·65			
		10^3x	8·3	13·2	25·1	34·9			
Ethanol	Benzene	v	2·18	2·15	1·93	1·35			
		10^3x	11·7	16·1	22·0	33·9			
	Heptane	v	6·80	5·76	4·33	3·78			
		10^3x	6·9	12·1	25·1	33·7			
	*cyclo*Hexane	v	6·96	5·67	3·93	3·26			
		10^3x	6·1	12·9	24·4	34·6			
Propanol	Benzene	v	1·97	1·80	1·63	1·53			
		10^3x	8·4	17·1	24·4	33·8			
	Heptane	v	6·05	5·60	4·64	3·43	3·18		
		10^3x	6·3	8·2	12·8	27·8	34·5		
	*cyclo*Hexane	v	6·03	5·18	4·15	3·60			
		10^3x	4·5	9·7	19·3	27·5			
Butanol	Benzene	v	2·46	2·29	2·12	2·00			
		10^3x	6·3	13·7	20·6	28·2			
	Heptane	v	5·66	4·55	3·29	3·05			
		10^3x	4·9	11·3	22·0	26·8			
	*cyclo*Hexane	v	7·01	5·46	4·22	3·70			
		10^3x	3·9	8·5	14·7	24·4			
Pentanol	Benzene	v	2·73	2·60	2·49	2·35	2·21		
		10^3x	7·4	9·9	12·4	21·9	27·4		
	Heptane	v	5·02	5·11	4·87	4·15	3·50	2·86	1·84
		10^3x	4·1	4·8	5·9	8·3	11·1	17·7	26·8
	*cyclo*Hexane	v	5·98	5·31	4·51	3·66			
		10^3x	3·9	8·3	13·8	24·5			
Hexanol	Benzene	v	3·20	2·95	2·79	2·54			
		10^3x	5·1	12·2	18·6	25·5			
	Heptane	v	5·03	3·90	2·64	2·27	1·78		
		10^3x	4·6	8·6	15·6	22·4	29·6		
	*cyclo*Hexane	v	6·42	5·97	4·95	4·90	4·12		
		10^3x	4·6	6·6	12·3	13·6	20·5		
Octanol	Benzene	v	3·82	3·61	3·41	3·34			
		10^3x	4·0	11·6	14·6	18·8			
	Heptane	v	3·61	3·12	1·90	1·36			
		10^3x	4·1	7·2	14·0	20·4			
	*cyclo*Hexane	v	7·00	6·22	5·19	4·15			
		10^3x	2·9	5·3	10·5	18·7			
Decanol	Benzene	v	4·63	4·55	4·54	4·41			
		10^3x	2·6	8·5	13·9	17·4			
	Heptane	v	2·27	1·64	1·06	0·43			
		10^3x	5·3	10·0	14·6	22·0			
	*cyclo*Hexane	v	7·52	7·37	7·09	6·21	5·80		
		10^3x	2·6	3·0	4·6	8·0	14·2		

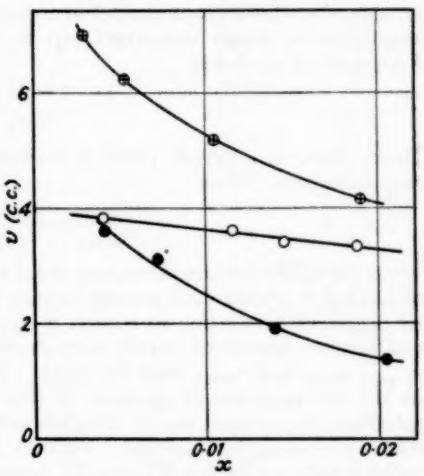
Tap *F* was closed, and the vessel turned anticlockwise through 90°. When the tap was opened, mercury refilled *B*. After repetition of this washing-out process, the tap was finally closed, and the vessel rocked for 5 minutes. The new position of the meniscus relative to a reference mark was then measured. The washing-out was repeated and the vessel rocked for a further 5 minutes, until constant readings were obtained, although usually there was no further change after the first period of shaking.

In a blank run in which a small amount of benzene (instead of an alcohol) was mixed with benzene, the apparent volume change did not exceed 10^{-4} c.c. It may be noted here that one disadvantage of the Keyes and Hildebrand apparatus, compared with ours, is that with the former, which has two capillaries, the measurement of a volume change requires twice as many readings. Moreover, with our apparatus it is easier to ensure that all readings of a set are made with the liquid under the same pressure, and in addition, since the space above the capillary is always saturated with solvent vapour, there is no possibility of solvent being lost by evaporation.

All measurements were made at 20·00° and the temperature of the thermostat was kept constant to ±0·001°. The necessity for careful control of the temperature will be evident from the fact that the volume changes measured were sometimes as small as 6×10^{-3} c.c.

The lower alcohols up to and including pentanol were purified by fractionation and finally dried over aluminium amalgam. The three higher alcohols were first purified by fractional crystallisation, dried in the same way, and distilled. Their b. p.s at 760 mm. were: methanol, 64·59°; ethanol, 78·36°; propanol, 97·15°; butanol, 117·61°; pentanol, 137·92°; hexanol, 157·12°; octanol, 193·2°; and decanol, 229·84°. The benzene used was a sulphur-free sample which had been purified by fractional crystallisation and fusion until its m. p. was 5·35°, corresponding to 0·26 mole-% of impurity. *cyclo*Hexane was free from benzene by treatment with nitrating mixture, and then fractionally crystallised. The m. p. of the final dry material was 6·05°, representing 0·26 mole-% of impurity. The heptane used was certified by the National Bureau of Standards as being 99·8% pure on a molar basis. As it blackened mercury slightly, it was shaken with mercury until reaction ceased and then distilled from phosphoric anhydride.

FIG. 2. *Plots of the volume increase per mole* (v) *of octanol, against the mole fraction* (x) *of the alcohol in the resulting solution.*



○ Benzene; ● heptane; ⊕ *cyclo*hexane.

Results.—The results are given in Table 1.

Discussion

For every alcohol in the concentration range studied the plot of v against x is apparently linear for the benzene solutions, whereas for the mixtures with heptane and *cyclo*hexane it is a curve convex to the x axis. This is illustrated in Fig. 2, in which are plotted the results for octanol.

From the experimentally determined relation between v and x for any one system, we may hope to draw conclusions about the value of v_1 (*i.e.*, the value of v when $x = 0$), and about the progressive association of the alcohol with increasing concentration, on which the shape of the v–x curve must depend. We shall consider the second matter first, since if, on the basis of assumptions about the association which are reasonable and consistent with other data, it proves possible to account for the experimental v–x curves, we then have a rational basis for the extrapolation to give v_1.

The very careful spectroscopic studies of solutions of alcohols in non-polar solvents carried out by Mecke and his collaborators (Kreuzer and Mecke, *Z. physikal. Chem.*, 1941, **49**, *B*, 309; Hoffmann, *ibid.*, 1943, **53**, *B*, 179; Mecke and Nückel, *Naturwiss.*, 1943, **21**,

248) have shown that the association begins by the formation, not of dimers, but of trimers. Their work also indicates that in the region of comparatively small alcohol concentrations with which we are concerned, it is a permissible approximation to neglect the formation of higher polymers, and also to apply the law of mass action in its ideal form to the equilibrium between monomer and trimer. Consider a solution containing $(1 - x)$ mole of solvent, and x mole of alcohol (*i.e.*, a total quantity of alcohol of xM g., where M is the g.-mol. weight of the monomer). If a fraction α of the alcohol A is associated to the trimer, then for the equilibrium constant K (on a mole-fraction basis) of the association $3A \rightleftharpoons A_3$, we have

$$K = \frac{\alpha(1 - 2\alpha x/3)^2}{3x^2(1 - \alpha)^3} \simeq \frac{\alpha}{3x^2(1 - \alpha)^3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Let us suppose that addition of M g. of alcohol to a large quantity of solvent would increase the volume by v_1 c.c. if all the alcohol were monomeric in the resulting solution, and by v_3 c.c. if all the alcohol were in the trimeric form. Let us further assume that v_1 and v_3 are constant (for a given alcohol in a given solvent at a fixed temperature) over the whole concentration range concerned (up to $x \simeq 0{\cdot}035$). Then the actual volume increase v per mole of alcohol is

$$\begin{aligned} v &= (1 - \alpha)v_1 + \alpha v_3 \\ &= v_1 - \alpha(v_1 - v_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2) \end{aligned}$$

Hence there is a simple relation between the values of v and α for any three alcohol concentrations. Thus

$$\frac{v_{0{\cdot}005} - v_{0{\cdot}01}}{v_{0{\cdot}005} - v_{0{\cdot}015}} = \frac{\alpha_{0{\cdot}01} - \alpha_{0{\cdot}005}}{\alpha_{0{\cdot}015} - \alpha_{0{\cdot}005}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where the subscripts are the values of x, *e.g.*, $v_{0{\cdot}01}$ is the volume increase in c.c. when one mole of alcohol is mixed with solvent to give a solution in which its mole fraction is 0·01 and its degree of association to trimers is $\alpha_{0{\cdot}01}$. For solutions of the alcohols in heptane and *cyclo*hexane, smoothed curves were drawn through the experimental points, from which $v_{0{\cdot}005}$, $v_{0{\cdot}01}$, and $v_{0{\cdot}015}$ were obtained. These gave the following values for the quantity on the left-hand side of equation (3) (the first figure of each pair refers to the *cyclo*hexane solutions, the second to the heptane solutions): methanol, 0·54, 0·555; ethanol, 0·55, 0·55; propanol, 0·575, 0·585; butanol, 0·665, 0·560; pentanol, 0·585, 0·610; hexanol, 0·610, 0·605; octanol, 0·615, 0·615; decanol, 0·565, 0·57. The mean value for *cyclo*hexane solutions is 0·59, and for heptane solutions 0·58. Divergencies from these are probably not greater than can be attributed to experimental error, except perhaps for butanol in *cyclo*hexane. If the value for this system is omitted, the mean of the *cyclo*hexane figures is 0·575.

Likewise, the quantity $\frac{v_{0{\cdot}005} - v_{0{\cdot}015}}{v_{0{\cdot}005} - v_{0{\cdot}025}}$ has a mean value of 0·67 (with extremes of 0·61 and 0·71) for the alcohols in heptane, and for methanol, ethanol, propanol, and pentanol in *cyclo*hexane a mean value of 0·635, with extremes of 0·67 and 0·62. (For butanol, the ratio is 0·79. The remaining three alcohols were not studied at sufficiently high concentrations for this ratio to be evaluated.)

Hoffmann (*loc. cit.*) has obtained spectroscopically a value for the equilibrium constant at 21·5° for the trimerisation of methanol in carbon tetrachloride. Combination of this with the heat of association given by Mecke and Nückel (*loc. cit.*) leads to a value of K of equation (1) of $2{\cdot}23 \times 10^3$ at 20°. Hoffmann further found that neither the nature of the alcohol (at least for the primary alcohols) nor that of the non-polar solvent (excluding benzene) has any very pronounced effect on the association. With this value of K, $\frac{\alpha_{0{\cdot}01} - \alpha_{0{\cdot}005}}{\alpha_{0{\cdot}015} - \alpha_{0{\cdot}005}}$ is 0·58, and $\frac{\alpha_{0{\cdot}015} - \alpha_{0{\cdot}005}}{\alpha_{0{\cdot}025} - \alpha_{0{\cdot}005}}$ is 0·66. In view of the agreement between these figures and those for the corresponding ratios involving v, we may say that for the *cyclo*hexane and heptane solutions, the dependence of v on x is consistent with the formation from the monomeric alcohol of trimers, with an equilibrium constant for the association of $\sim 2{\cdot}2 \times 10^3$ at 20°. We have accordingly calculated v_1 and $(v_1 - v_3)$ from equation (2),

using the experimental values of $v_{0\cdot005}$ and $v_{0\cdot01}$ and the α values corresponding to $K = 2\cdot23 \times 10^3$ ($\alpha_{0\cdot005} = 0\cdot116$, $\alpha_{0\cdot01} = 0\cdot265$). The figures for v_1 and v_3 so obtained are recorded in Table 2. The v–x curve for butanol in *cyclo*hexane shows more pronounced curvature than any other, and it may be that one or more of the experimental points is

TABLE 2. *Molar Volumes.*

(V_0 is the molar volume of the pure alcohol, $\overline{V}_\infty$ the partial molar volume in infinitely dilute solution. v_1 or v_3 is what the volume increase would be on mixing of one mole of alcohol with a large amount of solvent if the alcohol in the resulting solution were entirely monomeric or trimeric respectively. All volumes are in c.c. and refer to 20°.)

	Pure alcohols		In *cyclo*hexane			
	V_0	$\Delta V_0/CH_2$	v_1	v_3	$\overline{V}_\infty$	$\Delta\overline{V}_\infty/CH_2$
Methanol	40·49	17·87	3·75	2·05	44·25	22·25
Ethanol	58·36	16·43	8·15	0·5	66·5	14·95
Propanol	74·79	16·74	6·65	0·8	81·45	17·95 [a]
						17·15 [b]
Butanol	91·53	16·60	7·9 [a]	−2·6	99·4 [a]	
			7·05 [b]	−0·35	98·6 [b]	15·3 [a]
						16·1 [b]
Pentanol	108·13	16·61	6·6	0·75	114·7	
Hexanol	124·74	2 × 16·52	7·05	0·45	131·8	17·1
Octanol	157·78	2 × 16·48	7·15	0	164·95	2 × 16·6
Decanol	190·75		7·65	2·6	198·4	2 × 16·7

	In heptane				In benzene		
	v_1	v_3	$\overline{V}_\infty$	$\Delta\overline{V}_\infty/CH_2$	v_1	$\overline{V}_\infty$	$\Delta\overline{V}_\infty/CH_2$
Methanol	7·65	0·8	48·15	18·1	0·8	41·3	19·65
Ethanol	7·90	1·25	66·25	15·9	2·6	60·95	15·95
Propanol	7·35	−0·65	82·15	15·85	2·1	76·9	17·25
Butanol	6·45	0	98·0	16·2	2·6	94·15	16·85
Pentanol	6·05	−2·7	114·2	16·35	2·85	111·0	17·1
Hexanol	5·8	−2·25	130·55	2 × 15·7	3·35	128·1	2 × 16·8
Octanol	4·2	−2·25	162·0	2 × 15·85	3·95	161·75	2 × 16·8
Decanol	2·95	−2·1	193·7		4·65	195·4	

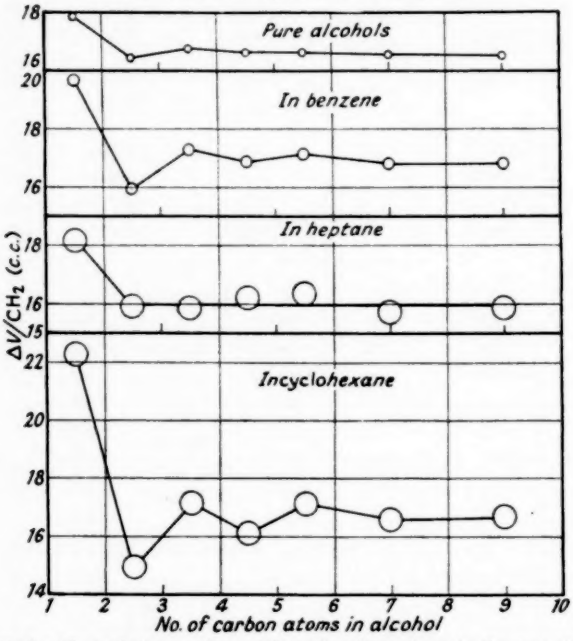
considerably in error. Accordingly, for this system two sets of values are given for v_1 and v_3. Those marked *a* are derived from $v_{0\cdot005} - v_{0\cdot01}$; those marked *b* from $v_{0\cdot01}$ and $v_{0\cdot015}$.

That the v–x curves for *cyclo*hexane and heptane solutions can be satisfactorily interpreted in terms of trimerisation cannot be regarded as a proof in itself that the association is in fact of this kind. The curves can be accounted for almost equally well if it is assumed that dimerisation is involved and a suitable equilibrium constant adopted. On this latter basis, v_1 values are obtained which are larger than those recorded in Table 2, and which are roughly the same as those obtained by free-hand extrapolation of the v–x curves. (On the trimerisation hypothesis, the v–x curves must have an initial slope of zero.) These larger values of v_1, however, still stand in the same relation to one another as those in Table 2, and their use would not alter the qualitative conclusions we shall draw from the values in Table 2.

For the benzene solutions the relation between v and x over the concentration range investigated is linear within experimental error, and we have therefore estimated the v_1 values given in Table 2 by direct extrapolation. We shall later show that these linear relations may, in a sense, be fortuitous. But as the slope of the experimental lines is comparatively small and the solutions examined are very dilute, it is unlikely that linear extrapolation gives values of v_1 which are seriously in error, or that its use leads to a false impression of the relation between the true values of v_1 for the different alcohols.

In Table 2, $\bar{V}_\infty$ is the partial molar volume of an alcohol at infinite dilution ($= v_1 + V_0$, where V_0 is the molar volume of the pure alcohol). $\Delta\bar{V}_\infty/CH_2$ is the increment in $\bar{V}_\infty$ on passage from one alcohol to its homologue. The changes in these increments (and also those in V_0) are shown in Fig. 3. It is difficult to assess the error in the values of $\Delta\bar{V}_\infty/CH_2$. The circles for the *cyclo*hexane and heptane solutions have been drawn with a radius representing 0·4 c.c., corresponding to an error of $\pm$0·2 c.c. in v_1. Those for benzene solutions have a radius representing 0·2 c.c., corresponding to an error of $\pm$0·1 c.c. in v_1. For butanol in *cyclo*hexane, as already explained, there is greater uncertainty in v_1. We have chosen the lower figure in Table 2 to evaluate the two increments which depend on it. The higher value of v_1 would make still more pronounced the differences between these increments and those which precede and follow them.

FIG. 3. *The relations between the increments per* CH_2 *group in* $\bar{V}_0$ *and in* $\bar{V}_\infty$ *in the three solvents as the homologous series is ascended.*



Each point is plotted midway between the number of carbon atoms in the two alcohols concerned. For the steps hexanol–octanol and octanol–decanol, the average increments have been plotted.

The following conclusions emerge from Table 2 and Fig. 3. (1) In all three solutions, and for the pure alcohols, the increment for methanol–ethanol is larger than for any subsequent step. (2) For the lower alcohols, the increments in V_0 show a slight alternation. This is more pronounced with the values of $\Delta\bar{V}_\infty/CH_2$ in benzene, and still more so in *cyclo*hexane. By contrast, in heptane, these increments from ethanol onwards are almost constant (within the probable limits of our experimental error). (3) If the step methanol–ethanol is excluded, the average increments in molar volume per CH_2 group are: in benzene, 16·8 c.c.; pure alcohols, 16·55 c.c.; in *cyclo*hexane, 16·5 c.c.; in heptane, 15·95 c.c. In other words, the space required by a CH_2 group in the hydrocarbon chain of a monomeric alcohol molecule is greatest in benzene solution, about the same in *cyclo*hexane as for the pure alcohol, and least in heptane, where it is almost identical with the corresponding quantity for the normal paraffins. (The average value of $\Delta V_0/CH_2$ from pentane to *n*-decane is 15·9 c.c.) (4) The mean value of $(v_1 - v_3)$ for *cyclo*hexane solutions is ~6·3 c.c., and for

heptane solutions ~7·0 c.c. Hence an alcohol molecule entering one of these solvents as a member of a trimer requires effectively considerably less space than if it enters as a monomer. In fact, if the higher alcohols could dissolve in heptane exclusively as trimers there would be an appreciable volume contraction. (5) In *cyclo*hexane and heptane, the values of v_3 (at least as far as hexanol) show an alternation.

We shall consider briefly the bearing of these results on the question which prompted the work, namely, whether monomeric alcohol molecules with sufficiently long chains tend to adopt coiled configurations in a favourable environment. If, in benzene and *cyclo*hexane solution, this tendency first appears with pentanol (the lowest alcohol capable of simulating a six-membered ring), then since this should lead to particularly economical packing of the alcohol molecules among the solvent molecules, we should expect a relatively low value of $\bar{V}_\infty$ for this alcohol and a correspondingly small value of $\Delta\bar{V}_\infty/CH_2$ for the step butanol–pentanol. Molecules of the next higher alcohol, hexanol, could presumably either tend to adopt a quasi-seven-membered ring structure, or a six-membered ring with one end of the molecule overlapping the ring. Some idea of the consequence of the second possibility may be obtained by considering the relationship of the molar volumes of a series of liquids such as benzene, toluene, *o*-xylene, and 1 : 2 : 3-trimethylbenzene; or *cyclo*hexane, methyl*cyclo*hexane, and ethyl*cyclo*hexane. For the three steps of the first group, the values of $\Delta V_0/CH_2$ are **17·55**, **15·1**, and **12·8** c.c.; for the second group, the increments are **19·7** and **17·6** respectively. The addition of a methyl group as a protuberance on a very symmetrical molecule causes a relatively large increase in V_0; further addition of a methyl group, or the enlargement of the first into an ethyl group, is accompanied by an appreciably smaller change in V_0 (cf. the abnormally large increments in V_0 and $\bar{V}_\infty$ for the step methanol–ethanol). If therefore a monomeric hexanol molecule in benzene or *cyclo*hexane tends to coil into a quasi-six-membered ring with one end of the molecule overlapping, we should expect to find this reflected in a relatively large $\bar{V}_\infty$, giving a large increment in $\bar{V}_\infty$ for the step pentanol–hexanol. But we should also expect that $\Delta\bar{V}_\infty/CH_2$ would be smaller for the next step, hexanol–heptanol.

These predictions are in fact consistent with the results summarised in Table 2 and Fig. 3. But the results cannot be regarded as proving the hypothesis, partly because of the omission of experiments on heptanol (which unfortunately could not be carried out in the time available for this work), and partly because the lower alcohols up to butanol show variations in $\Delta\bar{V}_\infty/CH_2$ as striking as those for the alcohols from butanol onwards. Nevertheless, the contrast between the trend in $\bar{V}_\infty$ for heptane solutions on the one hand, and that in benzene and, more strikingly, in *cyclo*hexane solutions on the other, shows how subtle the relation between solute and solvent molecules in such solutions must be, since, depending on the geometry of the solvent molecules and on the structure of the solvent, the partial molar volumes at infinite dilution of solutes such as primary alcohols sometimes show a steady increase per CH_2 group, and sometimes an alternating increase.

There is some evidence that alternation is also displayed by the apparent molar volumes of the alcohols in the trimeric state. The quantity $(V_0 + v_3)$ is the apparent volume occupied by the formula weight in grams of an alcohol if present in solution wholly as trimers. The increments in this quantity are :

	C_1–C_2	C_2–C_3	C_3–C_4	C_4–C_5	C_5–C_6	C_6–C_8	C_8–C_{10}
*cyclo*Hexane ...	16·3	16·75	15·6	17·7	16·3	2 × 16·3	2 × 17·8
Heptane	18·3	14·55	17·4	13·9	17·05	2 × 16·5	2 × 16·55

In both of these series, there is a regular alternation, at least as far as hexanol, and it is to be noted that this is now more marked for the heptane solutions, in which, by contrast, the values of $\Delta\bar{V}_\infty/CH_2$ are almost constant. Moreover, those steps (such as propanol–butanol), which in *cyclo*hexane give the smaller increments, give the larger increases in $(V_0 + v_3)$ in heptane. As it may be felt that little reliance can be placed on the values of $(V_0 + v_3)$ (since in the evaluation of v_3 a fixed mean value of the association constant was assumed), we may point out that the experimental v–x curves for the lower alcohols in these two solvents shown an alternation which is quite independent of the way in which

they have been analysed. The curvature of the plot for methanol is much less marked for *cyclo*hexane than for heptane; for ethanol, however, the heptane curve is the flatter of the two; for propanol, the position is again reversed, and so on. This alternation in the relative steepness of the two curves certainly persists up to, and including, pentanol.

There remains the question of the interpretation of the apparently linear relation between v and x for the alcohols in benzene. This can be accounted for if it is supposed that in the concentration range in question the alcohols are beginning to associate to dimers. But there seems no doubt from the spectroscopic work of Mecke and his collaborators (*loc. cit.*) that dimerisation does not occur at all. There is other evidence to support this. The careful freezing-point measurements by Peterson and Rodebush (*J. Phys. Chem.*, 1928, **32**, 709) on very dilute solutions of ethanol in benzene showed that up to a mole-fraction of ~0·004, the molecular weight is normal within ~2%. Accurate dielectric-constant measurements at 24·5° gave no indication of any association up to a mole fraction of 0·01 (Hoecker, *J. Chem. Physics*, 1936, **4**, 431). On the other hand, Beckmann's early freezing-point studies (*Z. physikal. Chem.*, 1888, **2**, 715) on more concentrated solutions showed that the apparent molecular weight starts to increase rapidly in the neighbourhood of $x = 0{\cdot}01$, and is nearly double the normal value when $x = 0{\cdot}04$. These facts suggest that the association of alcohols in benzene begins by the formation of higher aggregates than dimers (or even trimers), and, though Beckmann's results are not really sufficiently accurate for a definite decision to be made on this point, they do in fact agree better with the formation of tetramers than of trimers. We may also note that recently Weltner and Pitzer (*J. Amer. Chem. Soc.*, 1951, **73**, 2606) have pointed out that the virial coefficient data for methanol vapour are best interpreted in terms of tetramer formation. Furthermore, the aggregates formed in benzene, whatever they may be, differ from the trimers produced in other non-polar solvents in that, whereas the latter (from the rapid decrease of the molar polarisation as the concentration rises from zero) must have small or zero moment, the polymers in benzene must be highly polar, since the molar polarisation increases with alcohol concentration.

FIG. 4. *The course which would be taken by a plot of* v *against* x *if the alcohol was associated to tetramer (for assumptions see text).*

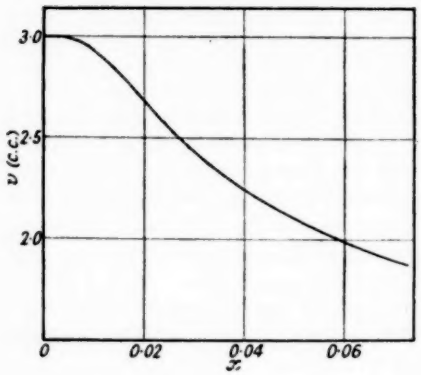


Fig. 4 is a plot of v against x calculated on the assumption that the alcohol is associated exclusively to tetramers. v_1 (the volume increase if a mole of alcohol goes into solution as the monomer) has been taken as 3 c.c.; v_4 (the volume increase if the same amount of alcohol dissolves as the tetramer) as 1 c.c.; and the equilibrium constant, *i.e.* (tetramer concn.)/(monomer concn.)^4, has been assumed to be 10^4 on a mole-fraction basis. The choice of these values is arbitrary, but the values for the two volumes are not unreasonable, nor, in the light of Beckmann's freezing-point data, is that for the equilibrium constant. It will be seen that the association of the alcohol is very slight when x is less than 0·01 : it is a little less than 1% when $x = 0{\cdot}006$. Over the range $x \simeq 0{\cdot}01$ to $\simeq 0{\cdot}035$ (*i.e.*, the concentration range covered in our experiments) the curve is nearly linear with a mean slope about equal to the average of those of the experimental lines. Finally, the shape of the curve at higher concentrations is very similar to that derived from Harms's density determinations (*loc. cit.*). At least, therefore, we may say that the available data, as a whole, are not inconsistent with the possibility that the initial association of the alcohols in benzene is by tetramer formation. It is hoped to carry out further experiments to test this provisional conclusion.

THE INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, September 28th*, 1951.]

80. *A Thermochemical Evaluation of Bond Strengths in Some Carbon Compounds. Part II.* Bond Strengths based on the Reaction* $CH_3I + HI \longrightarrow CH_4 + I_2$.

By R. J. Nichol and A. R. Ubbelohde.

Methods previously described for constant-pressure calorimetry for studying heat changes in Grignard reactions have been modified by use of carefully selected solvents having vapour pressures lower than that of ethyl ether, and by design of the reaction vessel so as to shorten the time required for attainment of thermal equilibrium.

Heat changes in the reactions

$$CH_3{\cdot}MgI + I_2 \longrightarrow CH_3I + MgI_2;\ Q_1 = -111{\cdot}91 \pm 0{\cdot}75 \text{ kcal./mole}$$

and

$$CH_3{\cdot}MgI + HI \longrightarrow CH_{4\,gas} + MgI_2;\ Q_2 = -125{\cdot}12 \pm 0{\cdot}61 \text{ kcal./mole}$$

(all in solution in *p*-xylene except $CH_{4\,gas}$)

give important thermochemical quantities which include the reaction (at standard pressure and 18°)

$$CH_3I + HI \longrightarrow I_2 + CH_4;\ Q_3 = -11{\cdot}04 \pm 1{\cdot}33 \text{ kcal./mole}$$

On this basis various bond energies can be calculated including a new value for $D(CH_3{-}I) = 54{\cdot}65 \pm 1{\cdot}70$ kcal. and $D(CH_3{-}H) - D(CH_3{-}I) = 45{\cdot}35 \pm 1{\cdot}37$ kcal./mole.

As described in Part I,* the use of a fairly simple constant-pressure calorimeter and carefully selected Grignard reactions permits the evaluation of certain bond energies not readily accessible in other ways.

The versatile possibilities of Grignard calorimetry made it desirable to check the basic procedure independently, before examining a greater variety of bond energies. In addition to the reactions described in Part I, the chemistry and calorimetry of the reaction

$$CH_3{\cdot}MgI + HI \longrightarrow CH_4 + MgI_2;\ Q_2 = -125{\cdot}12 \pm 0{\cdot}61 \text{ kcal./mole}$$

have now been studied. On account of the reaction of ethyl ether with hydrogen iodide and with free radicals, and also in order to minimise corrections for the vapour pressure of the solvent, the Grignard reactions were carried out substantially in *p*-xylene. The calorimeter was improved by constructing the reaction vessel of quartz which permits a much faster heat exchange than does glass, and by using a metal "adiabatic" mantle in place of a water-bath.

The calculated dissociation energy $D(CH_3{-}I) = 54{\cdot}65 \pm 1{\cdot}70$ kcal. overlaps the value obtained in Part I by use of other reactions and other methods of evaluation.

Other thermochemical results are referred to below.

Experimental

Preparation of the Grignard Solutions.—Except where otherwise specified, general methods of preparation and of protection against moisture, oxygen and light were as reported in Part I. To obtain the Grignard compound in xylene, 1 g. of pure dry vacuum-distilled magnesium was covered with 30 ml. of specially purified ether. After dropwise addition of 5 ml. of methyl iodide, reaction was completed by 15 minutes' refluxing. 300 Ml. of purified *p*-xylene were then added, and the ether together, with a little xylene was removed by distillation at 60°/13 mm. until no more ether distilled off. The *p*-xylene was purified by fractional freezing and final refluxing with sodium wire *in vacuo* for 3 hours. Analysis showed that the resulting xylene solutions contained approx. 1 mole of ethyl ether per mole of magnesium compound. For

* Part I, *J.*, 1948, 1161.

reasons described below, approximately 0·07 mole of dry anhydrous magnesium iodide was added to the stock solution per mole of methylmagnesium iodide.

We are indebted to Imperial Chemical Industries Limited, Billingham Division, for the very valuable help in supplying pure *p*-xylene. Other solvents tried and found less satisfactory for various reasons included *n*-hexane, anisole, dibutyl ether, dinonyl ether, acetaldehyde diethyl acetal, phenetole, and purified " technical " xylene.

Preparation of Solutions of Reagents in Xylene.—After trial of alternative methods, hydrogen iodide was prepared (Fig. 1*a*) by heating dry iodine (30 g.) in a round flask (500-ml. capacity) with decalin (300 ml.), freshly distilled to free it from peroxides, water, etc. The hydrogen iodide evolved was carried by a slow stream of oxygen-free nitrogen up the condenser, which retained most of any unchanged iodine, decalin, etc., and after passing through a tube packed with cleaned glass wool (to arrest iodine and decalin mist) was condensed in a wide U-trap cooled with solid carbon dioxide–alcohol. After no more reaction occurred in the decalin, as observed from the " clearing " of colour, the generator was removed and the crude solid hydrogen

FIG. 1*a*.

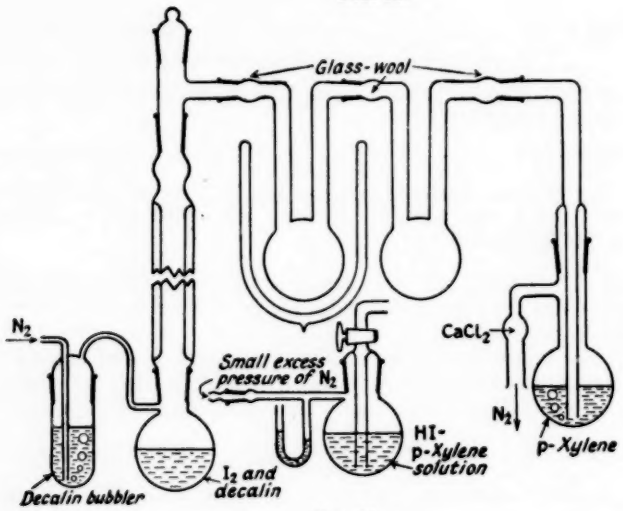


FIG. 1*b*.

iodide was redistilled into a second wide U-trap, in a slow current of nitrogen. Finally, the contents of the second trap, which were quite colourless, were allowed to warm to room temperature and were carried over by the nitrogen into about 300 ml. of pure dry *p*-xylene. The resulting solution was transferred for storage under slight excess pressure of nitrogen to a blackened vessel as illustrated in Fig. 1*b*.

In view of the photochemical decomposition of hydrogen iodide bright light was avoided throughout the preparation and storage. Before use of the solutions, minute traces of iodine which gave a weak sherry colour were removed by contact with a droplet of mercury. This stock solution (approx. 0·02N) was titrated at intervals, a pipette similar to that described in Part I being used. With all the precautions described, titrations reproducible within $\pm 0{\cdot}13\%$ could be obtained over a period of weeks.

Solutions of dry iodine in *p*-xylene were prepared by shaking and their titre also remained constant within an experimental error of $\pm 0{\cdot}1\%$ for several weeks.

Stoicheiometry of the Reactions.—

$$(a)\quad \underset{\text{in } p\text{-xylene}}{CH_3{\cdot}MgI,Et_2O} + \underset{\text{in } p\text{-xylene}}{HI} \longrightarrow \underset{\text{gas}}{CH_4} + \underset{\text{in } p\text{-xylene}}{MgI_2,Et_2O} \quad . \ . \ . \ . \ . \ (2)$$

The standard solution (20 ml.) of methylmagnesium iodide in xylene was transferred to the reaction vessel and three successive quantities of hydrogen iodide in *p*-xylene were pipetted in. The residual methylmagnesium iodide was then evaluated by Gilman's method.

In a typical experiment, the direct conversion of methylmagnesium iodide due to $0{\cdot}593 \times 10^{-3}$ mole of hydrogen iodide corresponded with $0{\cdot}591 \times 10^{-3}$ equivalent. This and similar tests showed that reaction (2) above, could be treated as quantitative under the conditions used for calorimetry. Before these tests had been carried out it had been feared that some of the hydrogen iodide might be carried off by the methane, but apparently owing to the excess of Grignard compound and the rapid reaction this possibility can be neglected.

FIG. 2. *Constant-pressure calorimeter.*

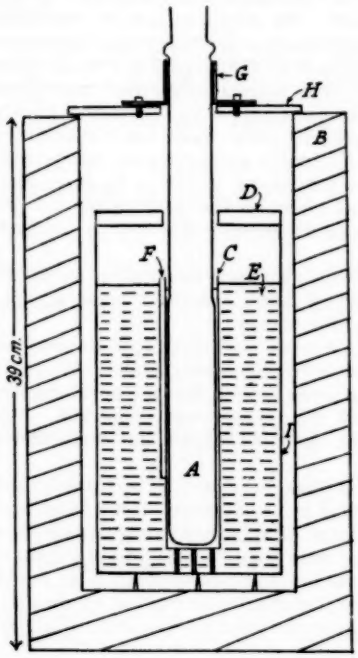
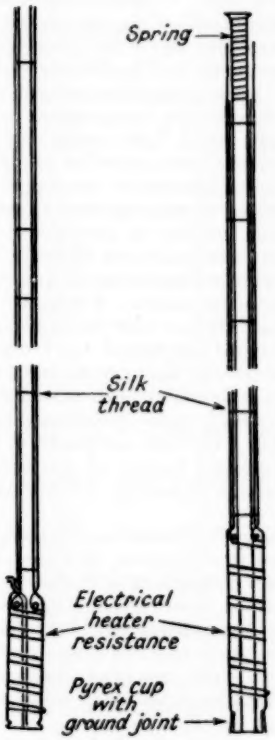


FIG. 3*a*. FIG. 3*b*.



Direct tests using combusion methods confirmed that methane was quantitatively evolved as a gas in accordance with equation (2).

$$(b)\quad CH_3{\cdot}MgI,Et_2O + I_2 \longrightarrow CH_3I + MgI_2,Et_2O \quad . \; . \; . \quad (1)$$
(all in *p*-xylene)

Tests based on those described in Part I showed that in the presence of excess of magnesium iodide added beforehand, as above, an amount of methylmagnesium iodide corresponding with $0{\cdot}537 \times 10^{-3}$ mole reacted with the disappearance of $0{\cdot}540 \times 10^{-3}$ mole of iodine. Under these conditions the alternative reaction (cf. Part I)

$$2CH_3{\cdot}MgI,Et_2O + I_2 \longrightarrow C_2H_6 + 2MgI_2,Et_2O$$

had a negligible influence on the calorimetry.

To make sure that no substantial attack on the solvent occurred in any of the these reactions, the methyl iodide formed in reaction (1) was determined by Zeisel's method after decomposition of the unchanged methylmagnesium iodide with dilute sulphuric acid: $0{\cdot}538 \times 10^{-3}$ mole of methyl iodide was recovered, which agreed within experimental error with the amount of methylmagnesium iodide used. In reaction (1) the magnesium iodide formed was retained

as a clear solution, presumably owing to the residual ethyl ether present. For accurate calorimetry this avoidance of solid phases whose heat content can depend on the state of division, etc., is an important feature.

The Constant-pressure Calorimeter.—To accelerate heat exchange a copper calorimeter (*C*, Fig. 2) (approx. mass 17·4 g.) was fitted with minimum clearance of about 1 mm. over the reaction vessel (*A*) which was made of quartz in view of its thermal conductivity being ten times that of Pyrex glass. A thin layer of silver was plated on to the quartz up to the shoulder. Paraffin (approx. 10 ml.) filled the space between the copper and the quartz to the shoulder of the reaction vessel. The adiabatic mantle (*B*) consisted of a cast aluminium block (approx. 27·3 kg.), and was fitted to reaction vessel by a brass lid (*H*) and an adiabatic collar (*G*); its temperature was kept by electrical heating within about $\pm 0{\cdot}04°$ of that of the calorimeter; a differential thermocouple and hand-controlled heating were used. By means of tests it was found that rather better estimations of heat exchange curves between the calorimeter and its surroundings with smaller root-mean-square deviations were obtained by filling part of the air space with carefully dried light magnesium carbonate (*E*). For convenience, this was packed in immediate contact with the calorimeter, in an intermediate copper pot (*I*) with a lid (*D*).

The temperature of the copper calorimeter was read to 0·004° by means of a single copper–constantan thermojunction, fitted into a pocket (*F*), and a galvanometer, lamp, and scale. Electrical heating for purposes of calibration was by means of a length of 40-gauge platinum–iridium wire (resistance $50{\cdot}887 \pm 0{\cdot}017$ ohms) wound direct on the reaction pipette (Fig. 3*a*). This wire remained bright and resistance measurements showed that it was unaffected by immersion in solutions of Grignard reagents.

Any heat flow down the walls of the quartz tube which connects the reaction vessel with the outside was minimised by keeping the closely fitting brass adiabatic collar at the same temperature as the brass lid and the aluminium adiabatic mantle.

For determining heats of solution of solid iodine in *p*-xylene at the appropriate concentration it was found more convenient to replace the pipette by the spring-loaded delivery vessel, (Fig. 3*b*). The solid was placed in the Pyrex cup which was ground into the upper container, so as to prevent ingress of the liquid around it, until the plunger was depressed. Alternate depression and raising of this plunger a few times led to rapid mixing and dissolution of the solid.

Heat of Vaporisation of Hydrogen Iodide from p-*Xylene Solution.*—This quantity, which is required in connection with one of the thermochemical cycles discussed below, was evaluated by direct determination of the equilibrium concentration of hydrogen iodide vapour above the solution, at three different temperatures. Bubblers were used to saturate a stream of dry oxygen-free nitrogen with the vapours at the temperature of the experiment. By duplicating these bubblers in series it was verified that saturation was effectively reached by means of two bubblers. The vapours in known volumes of gas were absorbed in standard alkali, and the concentration of hydrogen iodide was evaluated.

Heat of Vaporisation of Methyl Iodide from the Grignard Solutions.—A procedure corresponding to that for hydrogen iodide was used, with alcoholic silver nitrate as the analytical reagent. The remaining procedures and precautions were essentially as recorded in Part I.

Estimation of Residual Ether in p-*Xylene Solution.*—A solution (approx. 180 ml.) of methylmagnesium iodide in *p*-xylene, prepared as described above, was decomposed with *ca.* N-sulphuric acid (about 20 ml.; the requisite amount). The water and ether were separated from the resultant mixture by distillation. A few drops of *p*-xylene which distilled at the same time were separated, extracted with water, and rejected. The aqueous distillate and washings contained all the residual ether that may have been in the original solution. A method developed by the authors (to be published) for the determination of ether in aqueous solutions, based on the quantitative conversion of ether into acetic acid by acid potassium dichromate, was used. The residual ether in the *p*-xylene solution corresponded with approximately 1 mole per mole of the Grignard compound. This is probably held by co-ordination forces.

Accuracy of Electrical Calibration.—An input of electrical energy equivalent to $19{\cdot}10 \pm 0{\cdot}07$ cal. during $3\frac{1}{2}$ minutes gave a rise of $8{\cdot}03 \pm 0{\cdot}05$ arbitrary divisions on our scale. The energy was supplied from two 2-v accumulators in series through a platinum–iridium wire of approx. 40 gauge and with a resistance of $50{\cdot}887 \pm 0{\cdot}017$ ohm. The current from the accumulators had previously been passed through a similar resistance until a steady voltage was obtained. The chemical temperature–time curve was then matched electrically. The current through the heater wire was measured by means of the potential drop measurable to $\pm 0{\cdot}0001$ v across a standard resistance of 1 ohm in series with it.

Results and Discussion

The following heats of reaction were calculated from these observations (1 calorie = $4{\cdot}1833 \times 10^7$ ergs) :

$$\underset{0{\cdot}079\text{m}}{CH_3{\cdot}MgI,Et_2O} + \underset{0{\cdot}0192\text{m}}{I_2} \longrightarrow \underset{0{\cdot}00654\text{m}}{CH_3I} + \underset{0{\cdot}00654\text{m}}{MgI_2,Et_2O};\ Q_1 = -111{\cdot}91 \pm 0{\cdot}75 \text{ kcal./mole} \quad (1)$$

(all in *p*-xylene)

The probable mean error is calculated from the standard mean deviation of ten independent experiments.

$$\underset{\substack{0{\cdot}079\text{m}\\ \text{in}\\ p\text{-xylene}}}{CH_3{\cdot}MgI,Et_2O} + \underset{\substack{0{\cdot}0209\text{m}\\ \text{in}\\ p\text{-xylene}}}{HI} \longrightarrow \underset{\substack{\text{gas} +\\ p\text{-xylene}\\ \text{vapour}}}{CH_4} + \underset{\substack{0{\cdot}00711\text{m}\\ \text{in}\\ p\text{-xylene}}}{MgI_2,Et_2O};\ Q_2 = -125{\cdot}12 \pm 0{\cdot}61 \text{ kcal./mole} \quad (2)$$

Combination of (1) and (2), effects of small differences in molalities being neglected, gives equations for the cyclic process

$$\underset{\substack{0{\cdot}00654\text{m}\\ \text{in}\\ p\text{-xylene}}}{CH_3I} + \underset{\substack{0{\cdot}0209\text{m}\\ \text{in}\\ p\text{-xylene}}}{HI} \xrightarrow{Q_4} \underset{\substack{\text{gas} +\\ p\text{-xylene}\\ \text{vapour}}}{CH_4} + \underset{\substack{0{\cdot}0192\text{m}\\ \text{in}\\ p\text{-xylene}}}{I_2};\ Q_4 = -13{\cdot}21 \pm 0{\cdot}96 \text{ kcal./mole} \quad . \quad . \quad (3)$$

$$\downarrow q_1 \qquad \downarrow q_2 \qquad \downarrow q_3 \qquad \downarrow q_4$$

$$CH_3I_{gas} + HI_{gas} \xrightarrow{Q_3} CH_{4\,gas} + I_{2\,gas};\ Q_3 = -11{\cdot}04 \pm 1{\cdot}33 \text{ kcal./mole} \quad (4)$$

The gaseous reaction (4) can be calculated by evaluating the heat terms indicated in the cycle :

$$Q_3 = -13{\cdot}21 - (q_1 + q_2 + q_3 + q_4) \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In equation (5) the subsidiary thermal quantities were evaluated as described in the following paragraphs.

(i) In spite of the comparatively high dilution of the magnesium compounds, experiments showed that the differential heats of solution departed to a measurable extent from integral heats of solution. q_1 was therefore determined from directly measured partial pressures of methyl iodide over the solutions corresponding to the end-concentrations of the calorimetric reactions, at different temperatures. Concentrations found over the solution represented in equation (1) were, in 10^{-4} mole/l., 0·38 at 298° K, 0·317 at 293° K, and 0·298 at 291° K. This gives $q_1 = +6{\cdot}73 \pm 0{\cdot}52$ kcal./mole.

(ii) $HI_{p\text{-xylene}} \longrightarrow HI_{gas}$; $q_2 = 3{\cdot}03 \pm 0{\cdot}16$ kcal./mole. This was calculated by means of the Clausius–Clapeyron equation for the partial molal concentrations in the vapour over the solution. These were found to be $[HI] = 1{\cdot}976 \times 10^{-4}$ mole/l. at −1·2° C, $2{\cdot}120 \times 10^{-4}$ at 4·8° C, and $[HI] = 2{\cdot}480 \times 10^{-4}$ at 13·9° C, from which the partial pressures were calculated.

(iii) $CH_{4\,(gas\,+\,p\text{-xylene})} \longrightarrow CH_{4\,gas} + p$-xylene (liquid); $q_3 = -0{\cdot}12 \pm 0{\cdot}1$ kcal./mole. On the assumption that the methane was saturated with *p*-xylene, the partial pressure of methane at the temperature of the experiment was 751·13 mm. If pure methane is separated from the mixture by means of a semipermeable membrane at this pressure and is then compressed to 1 atmosphere, the work per mole done on the system is $293\boldsymbol{R} \log_e 760/751{\cdot}13 = 0{\cdot}0066$ kcal./mole. The heat liberated when the *p*-xylene is condensed back to liquid is $(8{\cdot}87/751{\cdot}13) \times 10{\cdot}11 = 0{\cdot}12$ kcal./mole, the heat of vaporisation for *p*-xylene being taken as 10·11 kcal. at 25° C (Pitzer and Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 803).

The overall correction q_3 is quite small. It becomes much more serious when more volatile solvents are used, such as ethyl ether or *n*-hexane. It may be noted that this

correction lapses when the products of reaction all remain in solution, as is the case in many possible applications of Grignard calorimetry.

(iv) $q_4 = (\Delta H_3 + \Delta H_4) = -11{\cdot}81 \pm 0{\cdot}75$ kcal., where, for $I_{2\,gas} \longrightarrow I_{2\,crystals}$, $\Delta H_3 = -14{\cdot}91$ kcal. (Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Rheinhold Publ. Corp., 1936) and, for $I_{2\,crystals}$ + *p*-xylene $\longrightarrow$ I_2(0·0192m in *p*-xylene), $\Delta H_4 = +3{\cdot}10 \pm 0{\cdot}75$ kcal. (our experiments). Insertion of these values into equation (5) gives:

$$Q_3 = -11{\cdot}04 \pm 1{\cdot}33 \text{ kcal./mole}$$

This new result may be used in conjunction with known bond dissociation energies. For example, equation (4) is interchangeable with

$$D(CH_3\text{–}I) + D(H\text{–}I) \longrightarrow D(I\text{–}I) + D(CH_3\text{–}H);\ Q_3 = -11{\cdot}04 \pm 1{\cdot}33 \text{ kcal./mole}$$

Combining this with the accurately known values (at 291° K) for $D(H\text{–}I) = 71{\cdot}58 \pm 0{\cdot}2$ kcal. and for $D(I\text{–}I) = 36{\cdot}27 \pm 0{\cdot}2$ kcal. (Bichowsky and Rossini, *op. cit.*) gives the *bond substitution* I *for* H *in methane*

$$D(CH_3\text{–}H) - D(CH_3\text{–}I) = 45{\cdot}35 \pm 1{\cdot}37 \text{ kcal.} \quad . \quad . \quad . \quad . \quad (6)$$

In view of the uncertainties of bond dissociations energies, this form of stating the result seems preferable at the present time. However, if our result (6) is combined with the known value

$$D(CH_3\text{–}H) = 101 \pm 1 \text{ kcal.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

(Szwarc, *Chem. Reviews*, 1950, **47**, 75), this gives

$$D(CH_3\text{–}I) = 54{\cdot}65 \pm 1{\cdot}7 \text{ kcal.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Allowance for the temperature coefficient of $D(CH_3\text{–}H)$ (cf. Kistiakowsky and Van Artsdalen, *J. Chem. Physics*, 1944, **12**, 478) seems premature in view of the uncertainty limits. Probable mean errors in individual results above are estimated on the basis of ten or more independent experiments. The probable mean error in equation (8) combines all the errors in the individual data according to standard procedure, and is an assessment of the overall reliability. It should not be confused with the mean deviation in a single type of experiment as quoted, *e.g.*, by Carson, Hartley, and Skinner (*Proc. Roy. Soc.*, 1949, *A*, **195**, 500).

The new value in (8) may be compared with previously published results.

(*a*) The value quoted by Mackle and Ubbelohde (Part I, *loc. cit.*). In Part I the heat value for the process $I_{2\,c} \longrightarrow I_{2\,gas}$ was taken as $18{\cdot}9 \pm 0{\cdot}25$ kcal. This was arrived at from the sum of *F*, the heat of fusion, and *V*, the heat of vaporisation of iodine as quoted by Bichowsky and Rossini (*op. cit.*, p. 25). In fact, *V*, as used by these authors, is a misprint for V_s (see Bichowsky and Rossini, *op. cit.*, p. 15). On this basis the correct value for the above process is 14·91 kcal. This has the effect of making $\frac{1}{2}q_2$, which is the relevant term in equation (19) of Part I, equal to 6·65 kcal. instead of 8·6 kcal., as hitherto employed. The final value for $D(CH_3\text{–}I)$ given in Part I is now modified to $52{\cdot}8 \pm 1{\cdot}4$ kcal.

(*b*) The value recorded by Carson, Hartley, and Skinner (*loc. cit.*) should be corrected to $54{\cdot}00 \pm 0{\cdot}5$ kcal on account of the modified $D(CH_3\text{–}H)$ value given in (7) above.

Both the results of Part I and of Carson, Hartley, and Skinner involve systematic uncertainties in a direction which tends to bring the calculations into closer overlap with those obtained by the present method. The chief systematic uncertainty in Part I is the value assumed for $D(CH_3\text{–}CH_3)$ (84·3 kcal./mole). If the upper probable limit (cf. Szwarc, *loc. cit.*) of 87 kcal./mole is used, this would make $D(CH_3\text{–}I) = 54{\cdot}2 \pm 1{\cdot}4$, calculated according to the procedures of Part I (see equation 19, p. 1169).

The chief systematic uncertainty in the procedure of Carson, Hartley, and Skinner lies in the calorimetric production of what may be imperfectly crystalline cadmium iodide from organic solvents (cf. also Hartley, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 1022). The lattice energy of cadmium iodide is about 190 kcal. An increased

heat content of 1% of this lattice energy, which is by no means unlikely in strained or otherwise imperfect crystals such as might be produced from organic solvents by precipitation, may be used to illustrate possible effects. Allowance for crystals imperfect to this extent would *increase* $D(CH_3–I)$ recorded by these authors to around 55·00 kcal., when the value $D(CH_3–H)$ is taken as 101 kcal. This overlaps our present value.

Attempts were also made to develop the methods of Part I by using ethereal solutions and solutions of hydrogen iodide in *n*-hexane (Mackle, Maniece, and Ubbelohde, unpublished observations). Vapour-pressure and other corrections left a rather large measure of uncertainty. The value of $D(CH_3–I)$ calculated from these unpublished observations was $57·6 \pm 3·2$ kcal., which gives quite independent support to our more accurate results now reported.

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81. *Lanthanon Complexes with Ethylenediaminetetra-acetic Acid. Part II.**

By R. C. VICKERY.

Complexes of the ammonium salt of ethylenediamine-*NNN'N'*-tetra-acetic acid with some members of the lanthanon series have been studied spectrophotometrically. Earlier work on these complexes has been extended, and the " internal " Stark effect splitting of the absorption spectra is shown to occur only with neodymium and erbium. Consideration is given to the suggestion that this phenomenon is due to a perturbation of the lanthanon ionic field, and this hypothesis is recast on the basis of lanthanon paramagnetism. Spectrophotometric data on the neodymium nitrilotriacetic acid complex are also presented.

THE value of complex formation in the separation of the lanthanons has recently been emphasised by Marsh (*J.*, 1950, 1879; 1951, 1461), studying the use of ethylenediamine-*NNN'N'*-tetra-acetic acid—" enta "—as its ammonium salt, in lanthanon separation. He paid particular attention to the use of ammonium enta in improved fractionations of mixtures of the heavy earths, whereas the author (Part I*) has studied its value in separation of the light lanthanons.

Moeller and Brantley (Illinois Univ. N60R1-71, Chem. Task VII, Sept. 1949; *J. Amer. Chem. Soc.*, 1950, **72**, 5447) studied the ammonium enta complexes of neodymium with particular reference to absorption spectra. Titration and ionic migration studies were also carried out to confirm conclusions drawn from the spectrophotometric data. The existence of a complex of 1 : 1 molar ratio of neodymium chloride and ammonium enta was postulated, and this has been confirmed by the preparative work of Marsh and of the author (*loc. cit.*). The possible existence of a further complex was discussed by Moeller and Brantley but the evidence for this was not considered conclusive; such data as were available related to complexes of different composition rather than the isomeric type for which evidence has been presented by the author (*loc. cit.*). Spectrophotometric studies on the neodymium complex carried out by Moeller and Brantley showed splitting of the main spectral absorption bands together with a shift of the bands towards longer wavelengths. This was ascribed to " an increase in the potential imposed on the system by the static symmetrical coulombic fields of the surrounding negative anions—the ' holohedric ' field potential "—which in turn was considered to indicate an increasing stability of structure. Tevebaugh (A.E.C.D. 2749; Declass., Nov. 1949) had similarly observed this " internal " Stark effect splitting in the absorption spectrum of citrate complexes of neodymium but considered the bands to be new entities and not derived from existing bands. This worker, moreover, observed band splitting only at comparatively high pH values, whereas it is known that the lanthanons and enta can form complexes at pH values in the region of 3·5—4·5.

* Part I, *J.*, 1951, 1817.

Glueckauf and McKay (*Nature*, 1950, **165**, 594) considered some aspects of complex formation in the actinon series to indicate possible *f*-shell covalency. By analogy, similar bonding might be expected in the lanthanon series, and this would be demonstrated by variation in absorption spectra. It might therefore be considered that the strong complexes formed between the lanthanons and citrate or enta ions may well involve electrons in the 4*f* shell. This would be in accord with the known increase in stability of the lanthanon complexes with increasing atomic number and filling of the 4*f* shell, but would not account for the formation of a yttrium complex (having no 4*f* electron) with a stability intermediate between those of the gadolinium and dysprosium complexes (Marsh; Vickery; *locc. cit.*).

Separations of the lanthanons with enta, carried out by Marsh (*loc. cit.*), and titration studies by the author (*loc. cit.*, and in preparation), show that the stability of lanthanon–enta complexes increases with atomic number, so that if, as Moeller and Brantley (*loc. cit.*) affirm, splitting of absorption spectra is concurrent with stability, then, on proceeding through the lanthanon series, splitting of spectral absorption bands on complex formation should become increasingly multiple. It is now shown that this premise is not confirmed.

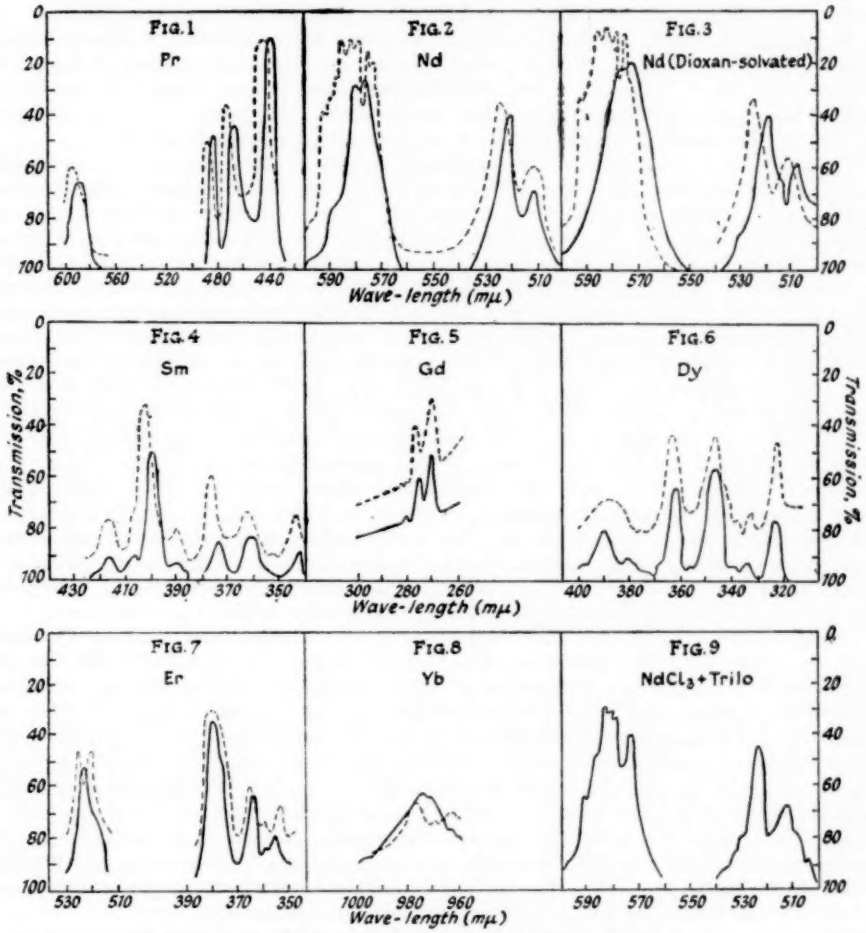
Alternatively, an increased shift of absorption bands towards longer wave-lengths might be expected with increasing stability; this has not been observed, but it must be remembered that Selwood (*J. Amer. Chem. Soc.*, 1930, **52**, 4308), in studying electron-shell deformation in concentrated solutions, found shifts to longer wave-lengths only in the light earths: europium and gadolinium absorption bands showed little movement, but those of holmium and erbium shifted towards the blue. Plumb, Martell, and Bersworth (*J. Phys. Coll. Chem.*, 1950, **54**, 1208) in spectrophotometric studies of various metal–enta complexes interpreted spectral displacements to the ultra-violet as due to complex formation, and Ephraim and Bloche (*Ber.*, 1926, **59**, 2692) considered shifts of absorption bands to the violet end of the spectrum to indicate compression of the 4*f* electron shell, and in studying lanthanon ammoniates found such a displacement to be at its maximum with praseodymium. Absorption shifts to higher wave-lengths on complex formation were attributed by Brode ("Chemical Spectroscopy," New York, 1939) to direct connexion of the additive group with the nucleus and formation of part of the chromophore; this would indicate a greater degree of chromophoric linkage with increasing shifts in absorption bands to lower frequencies. In the lanthanon series, however, the lighter, less firmly complexed elements show the greatest band shift towards lower frequencies. Brode's assertions cannot therefore be wholly tenable in this case; instead, there appears to be more correlation with the work of Selwood and of Ephraim and Bloche (*locc. cit.*) in that complexing initially distorts the electron shells by virtue of the potential of the surrounding anions, and that this is demonstrated by band displacement.

It is now apparent that, as the ionic radii of the lanthanons decrease with progression through the series, it becomes increasingly difficult for deformation of the electron shell to take place whilst at the same time the increase in electron density exerts an increasing binding effect on the electrons donated from the complexing agent. This would account for yttrium's taking up a position with lanthanons of similar ionic size, for the increase in stability of the complexes with atomic number, and for the collection together of the Sm–Eu–Gd triad.

Figs. 1—8 give data obtained with the Beckman spectrophotometer for 0·1M-solutions of lanthanon salts with and without the presence of 0·1M-ammonium enta. The shift of absorption to higher wave-lengths is seen to decrease with passage through the series, in conformity with Selwood's work (*loc. cit.*). Comparison of, *e.g.*, neodymium and erbium spectra at 510—530 mμ demonstrates that this band-shift is not merely a function of wave-length. Visual examination with a Hilger Barfit constant-deviation spectrometer indicated that shifts at band heads were always greater than at the tails so that, as well as the splitting in neodymium and erbium spectra, there is a tendency for overall widening of the band. The light earths were examined with chloride as the anion, and the heavy earths with perchlorate (Moeller and Brantley, *loc. cit.*; *Analyt. Chem.*, 1950, **22**, 433). Data obtained with the Beckman spectrophotometer showed band splitting to be detectable only in neodymium at the 576 mμ band and in erbium at the 523 mμ band. The expansion of

the dysprosium 388 mμ band with enta (Fig. 6) is possibly due to impurities of holmium and/or erbium but is further discussed below. The ytterbium spectrum is peculiar and might be anomalous, but was nevertheless consistently obtained with the solutions employed. In all cases except that of ytterbium, complexing with ammonium enta decreased the transmission at band heads.

Absorption spectra of lanthanons complexed with ethylenediaminetetra-acetic acid (1–8) and nitrolotriacetic acid (9).



Full lines ——— indicate normal absorption in 0·1M-solution.
Broken lines – – – – indicate absorption in 0·1M-complexed solution.
Chloride is the anion in 1–5 and 9, perchlorate is the anion in 6–8.

The splitting of the 576 mμ band of neodymium into four peaks (Moeller and Brantley, *loc. cit.*) was confirmed spectrophotometrically, but not that of the 522 mμ band although the band shift was present. The American workers made spectrophotometric readings at 20 Å band widths through the ultra-violet to 600 mμ and at 50 Å from 600 to 1000 mμ with smaller intervals at absorption band heads. In obtaining the data presented here, readings were in 15—20 Å band widths, with 10 Å widths between 10 mμ on each side of peaks. It is thus difficult to appreciate why 522 mμ band splittings were not observed

spectrophotometrically whilst that of the 576 mμ band was found. Visual spectroscopy showed no differentiation in the 522 mμ band.

It has been shown by Maley and Mellor (*Australian J. Sci. Res.*, 1949, *A*, **2**, 92) that the stabilities of chelated compounds are increased by the use of non-aqueous solvents. It was expected therefore that the partial replacement of solvent water by dioxan might invoke additional movement and splitting in absorption spectra. That this is so with neodymium is readily observed. The increased shift in dioxan solutions is obviously a solvent effect, whilst the higher degree of splitting observed is to be correlated with the fact that dioxan has only about one-fifth of the electrical moment of water.

As previously noted, optical examination of 4-cm. depth of enta-complexed solutions in the Hilger Barfit wave-length spectrometer gave no indication of splitting of the 522 mμ band of neodymium, but showed well the splitting of the 576 mμ band. No splitting of praseodymium and samarium absorption bands could be detected with the Beckman instrument, the Hilger-Barfit spectrometer, or the larger Littrow instrument.

The occurrence of detectable band splitting in only neodymium and erbium spectra among the lanthanons examined introduces interesting considerations. If we accept Moeller and Brantley's postulate that variations in band height and wave-length are attributable to increased potential (both hemihedric and holohedric) on the lanthanon ionic field, and that this also influences splitting of absorption bands, we have to explain the occurrence of this splitting only in neodymium and erbium spectra. Even if splitting of the absorption bands of other elements should be observed with instruments capable of higher resolution, it must still be determined why neodymium and erbium should display the strongest degree of band splitting. Neodymium and erbium, containing respectively three and eleven 4*f* electrons, may be considered the central members of their respective sub-groups in the lanthanon series. It is recognised that 0, 7, and 14 electrons in the 4*f* shell bestow a certain degree of stability upon the lanthanon configuration, and it is significant that neodymium and erbium, whose absorption spectra exhibit the greatest "internal" Stark effect, are the lanthanons most removed from these stable configurations. The apparent anomaly in the dysprosium 388 mμ band may well be viewed in this light as attributable to a Stark-effect splitting incompletely mature, even at the high position of this element on the magnetic susceptibility curve, owing to a residual tendency for dysprosium to revert to the stable gadolinium structure. In this respect studies on holmium and thulium absorption spectra might prove useful.

In studies of copper and nickel complexes, Russell, Cooper, and Vosburg (*J. Amer. Chem. Soc.*, 1943, **65**, 1301, 2329) found a linear relationship to exist between the magnetic moments and the maximum frequencies of light absorption. This would approximately correlate the splitting of neodymium and erbium spectra with the location of these two elements in the magnetic susceptibility curves for the lanthanons; but neodymium and erbium do not represent maxima in these curves as they do in absorption spectra: however, with the tendency of the absorption bands to shift to higher wave-lengths on complex formation, there might also exist a tendency for the magnetic-moment curves to shift to one side throughout the series on complex formation. Russell *et al.* showed that the magnetic susceptibilities of Ni^{2+} and Cu^{2+} decreased on complex formation, and it might well be, in the lanthanon series, that the susceptibilities similarly decrease where there is a tendency for the lanthanon ion to approach a stable configuration.

This premise has yet to be studied, but should its validity be shown, it would indicate an addendum to the suggestions of Van Vleck ("Theory of Electric and Magnetic Susceptibilities," Oxford Univ. Press, 1932) and Pauling ("The Nature of the Chemical Bond," Cornell Univ. Press, 1942) that, when the formation of a bond with a paramagnetic ion is accompanied by a small reduction in magnetic moment, it is the orbital contribution to the moment that is reduced. If therefore the internal Stark effect inducing the absorption-band splitting be attributable to an increase in the orbital contribution, it may thus indicate the possibility of hybrid bonding utilising the 4*f* electron level.

Similar to the use of enta in lanthanon fractionation was the earlier use by Beck (*Helv. Chim. Acta*, 1946, **29**, 357; *Mikrochem.*, 1947, **33**, 344; *Anal. Chim. Acta*, 1949, **3**, 41) of "trilo" (nitrilotriacetic acid ammonium salt). Although trilo cannot compete with

enta for efficiency of separation of the lanthanons, it was thought that a comparison of the absorption spectrum of the neodymium ion and of its complexes with trilo and enta (Fig. 2) would be of interest. It was not possible to obtain data for the complex in a water–dioxan system owing to the immiscibility of the water-solvated complex with dioxan, but Fig. 9 shows the absorption of the 0·1M-neodymium–trilo complex in water. Measurements were made as before, and again splitting and displacement of the 576 mμ band are apparent but not of the 522 mμ band. Intensity does not develop to the same extent as with the enta complexed ion owing to the smaller molecular size of trilo than of enta, but the "internal" Stark effect is nevertheless apparent. The band shift for the 576 mμ band in trilo is much greater than for enta, but there is negligible difference in the 522 mμ band shifts.

Experimental

The lanthanon oxides employed were of the following purities: lanthanum, >99·8; praseodymium, >99; neodymium, "Specpure;" samarium, >99·5; gadolinium, *ca.* 96; dysprosium, *ca.* 96; erbium, >96; ytterbium, *ca.* 99; yttrium, >99·8%; all other general reagents were of analytical quality. Enta had originally been derived from two sources: one, a sub-analytical grade, and the other, designated "Sequestrene AA" by the Alrose Chemical Co., U.S.A., much purer. Moeller and Brantley (*loc. cit.*) examined the absorption spectrum of the latter material and found no absorption in the visible and only background absorption in the ultra-violet from 270 to 210 mμ. In the Sequestrene used in this work transmission was of the order of 98% throughout the region examined. The sub-standard material employed for general separations showed transmission of 96·5—97·5% from 1000 to 400 mμ, decreasing then to 70% at 325 mμ. It is evident that care must be taken in the selection of enta supplies for spectrophotometric work: in the transmission values reported here corrections for adventitious absorption were made by utilising 0·1M-enta as the standard in the Beckman instrument. A noteworthy point is the solubility in water of the enta employed by Moeller and Brantley, who quote this as being "about 1%." Sequestrene AA is stated by the suppliers to be 0·03% soluble in water: this has been confirmed for the material employed in this work.

Absorption-spectrum studies were made on a Beckman DU quartz prism spectrophotometer.

0·2M-Solutions of the lighter lanthanons were prepared by dissolving the appropriate weight of oxide in hydrochloric acid, evaporating to dryness twice to remove excess of acid, and redissolving in water to 100 ml. volume. For the heavy earths, perchloric acid was used for dissolution, care being taken to use only just enough acid completely to dissolve the oxide with very little excess; the perchlorate solutions were used as prepared without intermediate evaporation to dryness.

0·2M-Ammonium enta was prepared by dissolving 7·84 g. of H_4 enta in dilute ammonia at 60°, boiling for 10 minutes to remove excess ammonia, cooling, and diluting to 100 ml. Absorption measurements were made on mixtures of 5-ml portions of lanthanon and enta solutions, so that the concentrations in the cell were 0·1M. for each component. Readings were standardised against 0·1M-enta. Absorption measurements of the uncomplexed lanthanons were made on 5 ml. of lanthanon solution plus 5 ml. of water, these readings being standardised against water.

When dioxan was to be introduced into the system, 10 ml. of 0·2M-lanthanon solution and 10 ml. of 0·2M-enta were mixed, evaporated to 10 ml., and diluted again to 20 ml. with redistilled dioxan. The solutions then examined were thus 0·1M with regard to both lanthanon and enta in 50% dioxan, and measurements were made against 0·1M-enta in 50% dioxan prepared in the same way with water replacing the lanthanon solution.

Spectrographic examinations were made through 4-cm. thickness of solutions prepared as above. The extent and accuracy of the spectrophotometric readings have been given above and the data obtained are shown in Figs. 1—8.

Data in the case of neodymium–trilo complex were similarly obtained and are shown in Fig. 9. 0·2M-Trilo was prepared by dissolving 4·06 g. of trilo in dilute ammonia, boiling off excess of base, cooling, and diluting the solution to 100 ml.

Thanks are due to Mr. J. Shelton for the spectrographic portion of this work, which was carried out as part of the research programme of the Division of Industrial Chemistry.

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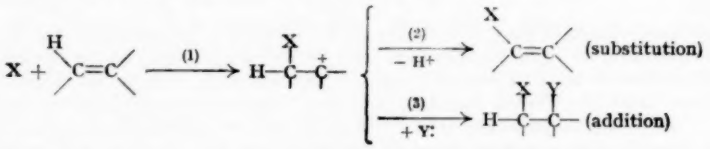
82. *Mechanism of Substitution and Rearrangement in Prototropic Systems. Racemisation and Hydrogen Exchange in Methylene-azomethines.*

By R. Perez Ossorio and E. D. Hughes.

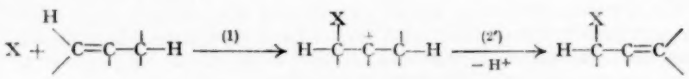
A brief résumé of heterolytic mechanisms in prototropic rearrangement and electrophilic substitution is presented. It is shown that the initial rates of hydrogen exchange and of racemisation in (+)-benzylidene-α-*p*-diphenylyl-benzylamine * are equal. Regard being paid also to a previous demonstration of the equivalence of the rates of racemisation and of isomerisation, the results establish that the synchronous, termolecular mechanism of bond-formation and bond-fission is applicable in this instance.

Of the possible forms of heterolysis of a carbon–hydrogen bond, *viz.*, R|··H (1*a*) and R··|H (1*b*) (the dots represent electrons), the type (1*a*), involved in nucleophilic substitution at the carbon centre, is relatively unimportant, mainly because of the low anionic stability of hydrogen. In simple, saturated aliphatic hydrocarbons, R–H, the form of heterolysis (1*b*), required for electrophilic substitution, may also be expected to be difficult. In a saturated carbon system, the valency electrons are mainly localised between two nuclei and are largely protected from electrophilic attack. Furthermore, a simple aliphatic alkyl group does not possess sufficient electron affinity to undergo easy separation from hydrogen by appropriating both of the electrons of the R–H bond.† In carbon-hydrogen bonds, therefore, special structural features are required for facile heterolysis, as we shall proceed to describe.

In an unsaturated system, the π-electrons are vulnerable to attack by a positive (electrophilic) entity, and the carbon cation, formed in this interaction, may suffer internal neutralisation with the loss of a proton to a base, *e.g.*,



In unsaturated aliphatic compounds, reaction with a nucleophilic reagent (3) may intervene, resulting in a partial or complete eclipse of the substitution process. In aromatic systems, the reaction corresponding to (2) is usually dominant and facile, doubtless because of the tendency, in $\overset{+}{\mathrm{Ar}}\!<\!\overset{\mathrm{H}}{\mathrm{X}}$, to reach the resonance-stabilised structure, ArX. In an olefin possessing a replaceable hydrogen atom in an attached alkyl substituent, the following change may also be formulated:

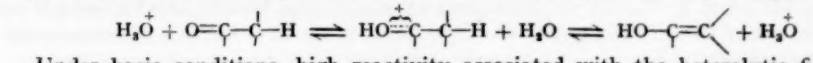


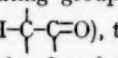
In general, the combination (1) and (2′) constitutes a reaction path for substitution with rearrangement, but, in the special case for which X = H^+, it also represents a mechanism of isomerisation (" three-carbon " prototropy in this instance). A concerted mechanism may also be envisaged, in which the first and second stages in the above scheme are fused

* In previous papers relating to this compound, Ingold *et al.* (see below) had named it as a derivative of benzhydrylamine, but as the term " benzhydryl " was discarded by the I.U.P.A.C. recommendations of 1949, the present name has been substituted.

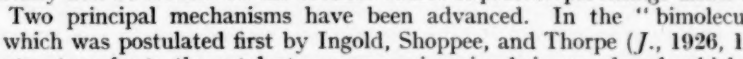
† In homolytic reactions, *e.g.*, Y· + R·|·H ⟶ Y–R + ·H, a high degree of polarisation or electron availability in the breaking bond is not such a vital condition. Consequently, the paraffinic hydrocarbons exhibit their most facile substitution reactions under conditions conducive to homolysis, *e.g.*, in halogenation processes in which halogen atoms participate (cf., especially, the observations of Kharasch and his co-workers in recent years).

into a single synchronous process. A similar mechanism applies to acid-catalysed prototropy in situations involving atoms other than carbon, *e.g.*, in carbonyl compounds :



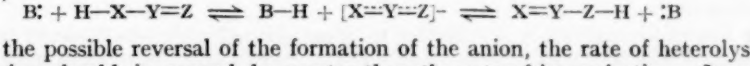
Under basic conditions, high reactivity associated with the heterolytic fission of a C–H bond at a saturated carbon centre may occur in the following way : If a powerful electron-appropriating group, for instance, a carbonyl, nitro-, or cyano-substituent, is present (*e.g.*, in ), the hydrogen atom will be more weakly held, and transfer of the proton may take place from the organic structure to the basic catalyst. This condition is well known in prototropic changes and in condensation processes, such as the aldol, Claisen, and allied types.

Attention may now be focused on the detailed course of prototropic change under basic conditions. Two principal mechanisms have been advanced. In the " bimolecular " mechanism, which was postulated first by Ingold, Shoppee, and Thorpe (*J.*, 1926, 1477), there is a proton transfer to the catalyst, a mesomeric anion being produced, which may recombine with a proton to form either the one or the other component of the tautomeric system, *e.g.*,



Because of the possible reversal of the formation of the anion, the rate of heterolysis by this mechanism should, in general, be greater than the rate of isomerisation. In evenly balanced tautomeric systems, the rates should clearly be notably different. If the partitioning of the anion is very unequal, the rate of isomerisation may be, depending on the direction of the inequality, nearly equal to, or much less than, the rate of heterolysis. Indications of some of the relationships to be expected from this mechanism have been obtained (see, especially, Ingold, Wilson, and co-workers, *J.*, 1936, 1328; 1938, 78; *Trans. Faraday Soc.*, 1938, **34**, 175; *J. Chim. phys.*, 1948, **45**, 232).

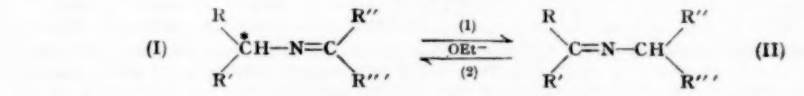
In the second mechanism, first advanced by Lowry (*J.*, 1927, 2554), the removal of one proton by a base is accompanied by the addition of another proton in a different position, the added proton being derived, for example, from the solvent or the conjugate acid of the base :



We shall henceforth be concerned mainly with evidence relating to this mechanism.

In this one-stage, termolecular mechanism, no intermediate entity is involved. Every molecule which suffers scission of the bond containing the mobile hydrogen atom should isomerise; the rates of isomerisation and of bond-fission should, therefore, be equal. Now, the rate of fission of a hydrogen–X bond, *e.g.*, in H–X–Y=Z, may be determined by measuring the rate of racemisation of an optically active structure with an asymmetric centre at X, and this may be compared with the chemically measured rate of isomerisation. Measurements of this type have been carried out in the methyleneazomethine systems (I⇌II) indicated in Table 1.

TABLE 1.



R	R′	R″	R‴	Equilm. ratio, (I) : (II)
(*a*) C_6H_5	CH_3	C_6H_5	*p*-Cl·C_6H_4	50 : 50 at 85°
(*b*) C_6H_5	CH_3	C_6H_5	C_6H_5	68 : 32 at 85°
(*c*) *p*-Ph·C_6H_4	C_6H_5	C_6H_5	H	56 : 44 at 25°
(*d*) *p*-MeO·C_6H_4	H	C_6H_5	H	24 : 76 at 74°

The relation between the chemically determined isomerisation rates and racemisation rates was studied in examples (*a*), (*b*) and (*c*) (Ingold and Wilson, *J.*, 1933, 1493; 1934, 93; Hsü, Ingold, and Wilson, *J.*, 1935, 1778). In each case, the rate of reaction (1), for example, was found to be equal to the rate of loss of optical activity at C* (see Table 1).

The observations therefore support the termolecular mechanism. The results exclude the bimolecular route for these compounds, for, since the intermediate should partly revert to the original structure in the balanced systems examined, the formation of a mesomeric anion requires that the rate of isomerisation should be lower than the rate of anionisation (or of racemisation).

Most informative evidence of mechanism may be derived by comparing the rate of isomerisation with the rate of exchange of hydrogen, which may be determined isotopically. Employing this method, a demonstration may be sought which includes the proof that in the H–X fission the hydrogen is lost to the solvent and not in an intramolecular manner. In a pure deuteroxylic solvent, which provides only deuterons, the termolecular mechanism requires that, for every original molecule once converted, one deuteron is admitted to the system in the concerted process. In the absence of other exchange mechanisms, there should therefore be initial equality between the rate of isomerisation of one tautomer and the rate of uptake of deuterium by the isomerising system. In the bimolecular mechanism, only a certain proportion of the intermediate anions lead to isomerisation, whereas, in a deuteroxylic solvent, anionisation should result always in the uptake of deuterons by the total isomerising system. For the latter mechanism, therefore, the rate of isomerisation of compounds such as those described in Table 1 should be lower than the rate of exchange of hydrogen.

An attempt to determine mechanism by using this principle was made by de Salas and Wilson (*J.*, 1938, 319) with system (*d*) (Table 1). Chemically measured isomerisation rates were compared with the rate of uptake of deuterium by the total system from an incompletely deuterated hydroxylic solvent. The relative rates of transference of protons and deuterons from the solvent to the solute system being undetermined, the results showed only that the initial rates of isomerisation and of hydrogen exchange were of similar magnitude. de Salas and Wilson were of the opinion that the results indicated a somewhat faster rate of deuterium exchange than of isomerisation, especially for compound (II) of example (*d*) (Table 1). Taking into account the equivalence of the rates of racemisation and of isomerisation—a result which had been demonstrated for methyleneazomethines—they suggested tentatively that a direct substitution mechanism at a single carbon centre was involved, this exchange proceeding without rearrangement and with retention of configuration and optical activity.

We now present the results of a rate comparison for system (*c*), *i.e.*,

(I) p-Ph·C$_6$H$_4$·CHPh—N=CHPh $\rightleftharpoons$ p-Ph·C$_6$H$_4$·CPh=N—CH$_2$Ph (II)

The equivalence of isomerisation rates and racemisation rates having been previously observed, the rate of loss of optical activity and the rate of uptake of deuterium, during the isomerisation of (I) under catalysis by ethoxide ions in the deuteroxylic solvent EtOD, were determined under strictly comparable conditions. The results are summarised in Table 2.

TABLE 2. *Racemisation and hydrogen exchange in benzylidene-α-p-diphenylylbenzylamine.*

Conditions: NaOEt (~ 0·1M) in dioxan–EtOD (2 : 1 by vol.) at 25°.

Time (hrs.)	6·0	17·0	29·5	53·5
Racemisation (%)	12·3	30·8	48·0	68·5
Exchange (%) *	11·9	31·0	58·4	93·3

* The results are calculated on the assumption that the isotope enters one position. An allowance is made to take account of a small proportion (0·9%) of ionisable protium in the heavy alcohol, the correction being applied on the assumption that protons and deuterons are transferred at the same specific rate. It is probable that protons are introduced at a faster rate than deuterons but the uncertainty introduced is unimportant when the available protium content of the medium is small. The change in the isotopic composition of the solvent during the progress of the reaction is disregarded.

The observations show that the rate of loss of optical activity and the rate of uptake of deuterium are initially approximately equal. Having regard also to the previously demonstrated equality between the rate of racemisation and the rate of isomerisation (Hsü, Ingold, and Wilson, *loc cit.*), it may be concluded that the termolecular mechanism is operative for this compound under basic conditions. The divergence between the rate of

racemisation and the rate of exchange in the later stages of reaction (Table 2) provides no evidence against this conclusion. Near the beginning of the isomerisation of (I), practically all the formed (II) will have gone through the simple history (I) ⟶ (II), which allows only one deuterium atom to enter a molecule of (II). Later, some (II) will be present which has gone through a more complicated history, such as (I) ⟶ (II) ⟶ (I) ⟶ (II), providing for the admission of more than one deuterium atom into one molecule of finally formed (II).*

The optical results for the racemisation process, which adheres to a first-order rate law with respect to the optically active compound (cf. Hsü, Ingold, and Wilson, *loc. cit.*), are unaffected by such complications. This also is consistent with our deduction, though it is not, in itself, diagnostic of mechanism. Loss of optical activity being the result of fission of the C–H bond at the asymmetric centre, the rate of racemisation should be independent of any subsequent changes in the initial (inactive) product. Thus, the optical measurements refer throughout the course of reaction to the simple conversion (I) ⟶ (II), and, since the concentration of the basic catalyst is constant during the change, and the medium conditions are uniform throughout, the rate of racemisation varies only with the concentration of the optically active compound.

While the results establish the termolecular mechanism, and leave little scope for alternative suggestions in this instance, it should be emphasized that a different situation obtains in other cases (cf., especially, Ingold, Wilson, and co-workers, *locc. cit.*; Swain, *J. Amer. Chem. Soc.*, 1950, **72**, 4578; Bell and Clunie, *Nature*, 1951, **167**, 363). It is also clear that, for the reaction which we have investigated, there is no evidence of hydrogen exchange by electrophilic substitution without rearrangement.

Experimental

(±)- and (+)-Benzylidene-α-*p*-diphenylylbenzylamine were prepared as described by Hsü, Ingold, and Wilson (*locc. cit.*).

The Catalyst Solution.—The same solution, made from sodium (0·21 g.), dioxan (48 c.c.), and deuterium ethoxide (24 c.c.), was used in the exchange and racemisation experiments. Deuterium ethoxide of 99% isotopic purity was obtained as follows: Sodium (11·5 g.) was melted under decalin in a three-necked flask, fitted with a stirrer, a dropping-funnel, and a condenser. After being shaken and cooled to 60°, the " powdered " metal was treated with dry alcohol (23 g.), and the contents of the flask were stirred and heated under reflux for six hours. The condenser was then turned downwards, and the temperature was gradually increased to 170—180° to eliminate any traces of alcohol. Deuterium oxide (99·6% D_2O; 10 g.) was added under reflux during one hour, and the mixture was heated, with stirring, at 120—130° for two hours. The deuteralcohol was distilled, dried by successive distillations from fused barium oxide and sodium, and fractionated from traces of decalin. The yield of purified material was 80%, and the estimation of ionisable deuterium, as described by Ingold, de Salas, and Wilson (*J.*, 1936, 1328), showed that the sample contained 99·1 mols. % of deuterium ethoxide.

Exchange Experiments.—Portions of a solution (0·2M) of (±)-benzylidene-α-*p*-diphenylylbenzylamine in the catalyst medium were enclosed in sealed tubes and kept for various times at 25·0°. The azomethines were isolated, and analysed for deuterium, as described by de Salas and Wilson (*locc. cit.*; cf., *J.*, 1934, 493, 1593; 1936, 1550). The results are given in Table 2.

Racemisation Experiments.—(+)-Benzylidene-α-*p*-diphenylylbenzylamine (1·25 g.) was dissolved in 20 c.c. of the catalyst medium and the rotation (initially, $\alpha_D^{25} = 0{\cdot}53°$) was followed in a 2-dm. jacketed tube kept at 25·0°. The first-order rate coefficient, obtained from the plot of log α against *t*, was 0·0217 hr.$^{-1}$.

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* An experiment in which the tautomeric system was left in contact with the medium for a period approaching the time required for total reaction showed that the deuterium content, calculated on the basis of exchange in one position only, was 180%. The medium contained an appreciable proportion of available protium at this point, and this figure, which has not been corrected for isotopic impurity, is expected to be lower than the value corresponding to complete exchange (200% for two replaceable hydrogen atoms).

83. *The Basic Strengths of Some* N-4-*Diphenylylamidines.*

By D. J. Carswell, J. Cymerman, and L. E. Lyons.

The basic strengths of a series of *N*-4-diphenylylamidines (*p*-Ph·C_6H_4·NH·CR:NH; R = alkyl, alicyclic and aryl groups) have been determined by potentiometric titration in 50% aqueous alcohol, and the results are discussed.

It is becoming increasingly evident that an understanding of the relation between chemical constitution and anti-bacterial activity in any given series of compounds cannot be reached without an investigation of certain physico-chemical factors, notably the percentage of compound ionised at the physiological pH (7·2), the surface area of the molecule, and its partition between lipoid and aqueous phases (Albert, Rubbo, *et al.*, *Brit. J. Exptl. Path.*, 1945, **26**, 160; 1949, **30**, 159). Albert *et al.* (*locc. cit.*) were able to demonstate in the case of the acridine anti-bacterials that a pK_a of about 7·8 at 20° was a prerequisite for high bacteriostatic activity, and that this resided mainly in the cations; anions and undissociated molecules had little activity.

In view of the known antituberculous activity of 4-aminodiphenyl and β-naphthylamine (Erlenmeyer *et al.*, *Helv. Chim. Acta*, 1945, **28**, 1406; 1947, **30**, 2058; Doub and Youmans, *Amer. Rev. Tuberc.*, 1950, **61**, 407), which are both weak bases (pK_a 4·27 and 4·3 respectively at 25°; Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472; Farmer and Warth, *J.*, 1904, 1726), a series of *N*-4-diphenylylamidines *p*-Ph·C_6H_4·NH·CR:NH was prepared (Bauer and Cymerman, *J.*, 1950, 1826) and the determination of the ionisation constants of the 12 bases involved is reported herein.

Method.—pK_a values were obtained by potentiometric titration, using the procedure of Albert and Goldacre (*J.*, 1946, 706) with some modifications. Since the bases concerned are insoluble in water, they were titrated by running 50% aqueous-ethanolic N/20-hydrochloric acid into a solution of the base (3—25 mg., *ca.* 0·0001 mole) in 50 c.c. of 50% aqueous alcohol. Carbon dioxide-free distilled water and absolute alcohol were used as solvents. The solution was contained in a water-jacketed (20° ± 1°) beaker containing the glass and the calomel electrode supplied with the Leeds and Northrup Universal pH meter. The titration was carried out in a nitrogen atmosphere, a rapid stream of the gas being introduced directly below the microburette and serving as an efficient stirrer. The pH meter was checked against buffer solutions at pH 4·0, 7·1, and 9·2. All titrations were carried out in duplicate at 20° ± 1°; it has been shown (Hall and Sprinkle, *loc. cit.*; Albert and Goldacre, *loc. cit.*) that the temperature coefficient of basic strength in both aqueous and 50% alcoholic solution is of the order −0·01 to −0·03 unit per degree, and would thus not affect the experimental accuracy in these determinations.

Results.—The amidines being strong bases gave good end-points represented by a steep drop in the smooth curve relating pH to the quantity of acid added.

Calculations were carried out by using equation (1) which takes into account the effect of hydroxyl ion; in the low concentrations used this correction becomes appreciable at pH values exceeding 9. When thus corrected, pK_a values showing a mean deviation of from ±0·04 to 0·06 unit were obtained.

$$pK_a = pH - \log \frac{[B] - [OH^-]}{[BH^+] + [OH^-]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

A typical result (for *N*-4-diphenylylhexanamidine) is as follows :

% neutralised	19	25	32	38	44	51	57	63	70	76	82	89
pK_a	9·31	9·28	9·29	9·30	9·29	9·28	9·24	9·26	9·26	9·26	9·24	9·24

In one case, for *N*-4-diphenylylheptadecanamidine, solubility was exceedingly low. The effect of 50% alcohol on ionisation of bases is known to be a depression of basic strength by 0·5—1·0 unit from the pK_a measured in water (Mizutani, *Z. physikal. Chem.*, 1925, **118**, 327; Hall and Sprinkle, *loc. cit.*) and it is assumed (Dippy, *Chem. Reviews*, 1939, **25**, 151; Bennett and Glasstone, *J.*, 1935, 1821) that a series preserves the same order of basicity in dilute alcohol as in water. Since the relation between pK_a and percentage of ethanol is a smooth curve, the

value of pK_a for the heptadecanamidine in 50% alcoholic solution could be deduced by extrapolation from the results obtained for the compound in 80, 70, and 60% alcoholic solution. Low solubility, however, did not permit carrying out the potentiometric titration in 70% and 60% alcoholic solution; only the value in 80% ethanol could be obtained. The pK_a was therefore determined in both 80% and 50% alcoholic solution by measurement of the pH at the exact half-neutralisation point. The results are collected in the Table 1.

TABLE 1. *Ionisation of* N-4-*diphenylylamidines,* p-Ph·C_6H_4·NH·CR:NH (I), *in* 50% *alcohol at* 20° ± 1°.

R	pK_a	R	pK_a
(*a*) Me	9·26	(*c*) Ph	8·10
	9·17 [1]	*p*-Ethoxyphenyl	8·25
n-C_5H_{11}	9·26	3 : 4-Dimethoxyphenyl	8·21
n-C_7H_{15}	9·14	*p*-Chlorophenyl	7·60
n-$C_{16}H_{33}$	9·06 [1]	*p*-Carbethoxyphenyl	7·22
	9·12 [2]		
	9·17 [3]		
(*b*) *cyclo*Hexyl	9·20		
*cyclo*Pent-1-enyl	8·66		
*cyclo*Hex-1-enyl	8·85		

[1] In 80% alcohol by potentiometric titration. [2] In 80% alcohol from half-neutralisation point. [3] In 50% alcohol from half-neutralisation point.

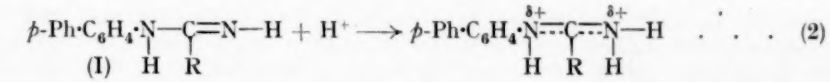
TABLE 2. *Ionisation of primary aromatic amines at* 20° ± 1°.

Substance	pK_a in 50% ethanol	pK_a in water	ΔpK_a
Aniline	4·33 ± 0·05	4·65 [1]	0·32
2-Aminodiphenyl	3·39 ± 0·05	3·84 [1]	0·45
3-Aminodiphenyl	3·97 ± 0·05	—	—
4-Aminodiphenyl	4·05 ± 0·05	4·34 [1]	0·29

[1] Hall and Sprinkle, *loc. cit.*

The basic strengths of four related primary aromatic amines, *viz.*, aniline, and 2-, 3-, and 4-aminodiphenyl, were also determined in 50% alcoholic solution, and the results are recorded in Table 2, together with the results of Hall and Sprinkle (*loc. cit.*) for 3 of these amines in aqueous solution. It is seen that ΔpK_a lies between 0·29 and 0·45.

Discussion.—Addition of the proton may be written as in equation (2); there is a charge distribution in the cation but, although δ+ is used twice, it is not true to say that δ+ at the one centre equals δ+ at the other, although of course the sum equals the charge



. . . (2)

on a proton. Amidines, having two equivalent structures contributing to the amidinium ion, will therefore possess high basic strengths; thus acetamidine and benzamidine have pK_a 12·52 (Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162) and 11·6 (Albert, Goldacre, and Phillips, *J.*, 1948, 2241) at 20° respectively. The basicity of a series of substituted benzamidines has been determined potentiometrically by Lorz and Baltzly (*J. Amer. Chem. Soc.*, 1949, **71**, 3992) by titrating solutions of their hydrochlorides in 50% methanol with 0·1N-sodium hydroxide.

All the amidines examined in the present work are moderately strong bases; the differences observed are explicable on existing theory. In compounds of series (*a*) (I; R = alkyl), in which R is a group with a $-I$ effect, the ionisation potential of the nitrogen atom is decreased and thus the basic strength of the parent compound (I; R = H) should be exceeded by the substituted compounds, as is shown, *e.g.*, by the greater basic strength of *n*-alkylamines compared with ammonia (Hall and Sprinkle, *loc. cit.*). Unfortunately the compound (I; R = H) could not be obtained. In the series (I; R = *n*-alkyl) it is known that the -*I* effect increases as the length of the *n*-alkyl chain increases, *e.g.*, *n*-amyl is more strongly $-I$ than methyl but, that although this second-order inductive effect is relayed along the chain of carbon atoms, it is weaker than the primary inductive effect and

is rapidly attenuated by about two carbon atoms in a *n*-alkyl chain. Thus while the pK_a of ammonia is 9·27 at 25°, the values for the five *n*-alkylamines from methyl to *n*-amyl all fall within the narrow range 10·62 ± 0·05 (Hall and Sprinkle, *loc. cit.*), and undecylamine, dodecylamine, and hexadecylamine all have pK_a 10·7 at 25° (Hoerr, McCorkle, and Ralston, *J. Amer. Chem. Soc.*, 1943, **65**, 328). In the same way, the pK_a values for the compounds (I; R = CH_3, *n*-C_5H_{11}, *n*-C_7H_{15}, and *n*-$C_{16}H_{33}$) all fall within the range 9·20 ± 0·06. Compounds of series (*b*) (I; R = alicyclic) show the olefinic groups to have a $+E$ effect as expected, and the *cyclo*hexyl group is seen to have aliphatic character.

Series (*c*) (I; R = aryl) exhibits a $+E$ effect due to the aryl group, together with the effect of the substituent attached to the phenyl group. Alkoxy-substituents are classified (Dewar, "Electronic Theory of Organic Chemistry," Oxford, 1948) as showing a $-E$ effect and this is consistent with the results quoted for the ethoxy- and the dimethoxy-compound. The pK_a's of the other compounds are consistent with $-E$ and $+I$ effects of the chloro-group, the former being the greater, and with $+E$ and $+I$ effects of the carbethoxy-group.

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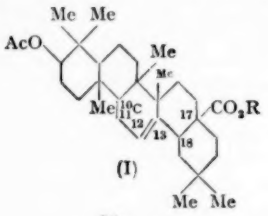
84. *Triterpene Resinols and Related Acids. Part XXV.* Ketoisooleanolic Acid and* iso*Oleanolic Acid.*

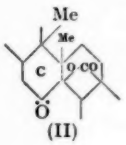
By L. C. McKEAN, WILLIAM MANSON, and F. S. SPRING.

The αβ-unsaturated keto-acid obtained by hydrolysis of acetylketo-oleanolic lactone (II) is shown to be acetyl-12-keto-olean-10-enolic acid (V; R = H), and the methyl ester (V; R = Me) of this acid is shown to be identical with the product obtained by bromination of methyl acetyldihydro-keto-oleanolate (IV). Catalytic reduction of this ester gives methyl acetylolean-10-enolate (XII; R = Me) isomeric with methyl acetyloleanolate (methyl acetylolean-12-enolate) (I; R = Me), with methyl acetylmorolate (methyl acetylolean-18-enolate) (XV), and with methyl δ-acetyloleanolate [methyl acetylolean-13(18)-enolate] (XIII; R = Me).

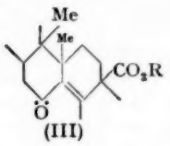
ACETYLKETO*iso*OLEANOLIC ACID was prepared by Kitasato (*Acta Phytochim.*, 1935, **8**, 315) by treatment of acetylketo-oleanolic lactone (II) with hydrogen bromide in acetic acid, and later by Ruzicka, Cohen, Furter, and Sluys-Veer (*Helv. Chim. Acta*, 1938, **21**, 1735) by treatment of the lactone (II), which can be obtained by several routes from acetyloleanolic acid (I; R = H), with hydrogen bromide in ethanol. Acetylketo*iso*oleanolic acid was



(I)



(II)



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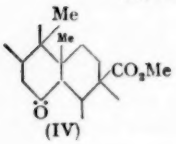
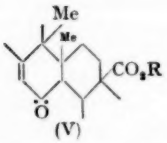


(IV)



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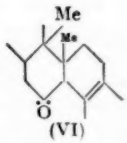
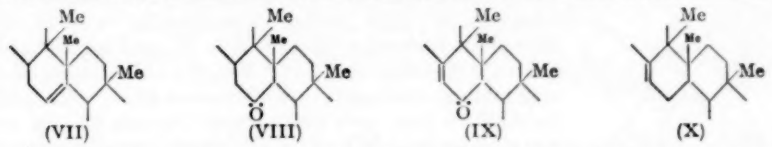


(VI)

* Part XXIV, *J.*, 1951, 3336.

provisionally represented by the formula (III; R = H) by Ruzicka *et al.* (*loc. cit.*), and this formula received support from the behaviour of the acid on treatment with boiling quinoline, an isomeric neutral compound being obtained, presumably by lactonisation between the carboxyl group and the double bond.

According to Picard, Sharples, and Spring (*J.*, 1939, 1045) methyl acetylketo*iso*-oleanolate can be prepared from methyl acetyloleanolate (I; R = Me) by oxidation to methyl acetyldihydroketo-oleanolate (IV) (Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804) followed by bromination of the last. Bromination of β-amyranonyl acetate (VIII) which differs from methyl acetyldihydroketo-oleanolate (IV) solely in the nature of the attachment at $C_{(17)}$ and which is obtained by oxidation of β-amyrin acetate (VII), gives *iso*-β-amyrenonyl acetate which has been shown to be 2-acetoxyolean-10-en-12-one



(IX) (Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019). By analogy the structure of methyl acetylketo*iso*oleanolate will be (V; R = Me). Of the alternative formulæ (III; R = H) and (V; R = H) for acetylketo*iso*oleanolic acid, the latter is not in harmony with the behaviour of the acid when treated with quinoline. The formation, under these conditions, of an isomeric lactone requires that the carboxyl group and ethylenic linkage of acetylketo*iso*oleanolic acid be relatively close to each other (probably $\beta\gamma$- or $\gamma\delta$-unsaturated acid). On the other hand, comparison of the optical rotations of the corresponding oleanolic acid and β-amyrin derivatives (see table) supports the view that *iso*-β-amyrenonyl acetate (IX) and acetylketo*iso*oleanolic acid differ only in the nature of the substituent attached to $C_{(17)}$, *i.e.*, that acetylketo*iso*oleanolic acid is acetyl-12-keto-

β-Amyrin acetate (VII)	+81°[1]	Acetyloleanolic acid (I; R = H)	+75°[1]
		Methyl acetyloleanolate (I, R = Me)	+70°[1]
β-Amyranonyl acetate (VIII)	−15°[2]	Methyl acetyldihydroketo-oleanolate (IV)	−11°[3]
iso-β-Amyrenonyl acetate (IX)	+61°[2]	Acetylketo*iso*oleanolic acid	+61°[4]

[1] Elsevier, "Encyclopædia of Organic Chemistry," 1940, Vol. XIV, pp. 533, 540. [2] Budziarek, Johnston, Manson, and Spring (*loc. cit.*). [3] Picard and Spring, *J.*, 1940, 1387; Ruzicka and Cohen, *loc. cit.*; Dietrich and Jeger, *Helv. Chim. Acta*, 1950, **33**, 711. [4] Ruzicka, Cohen, Furter, and Sluys-Veer, *loc. cit.*

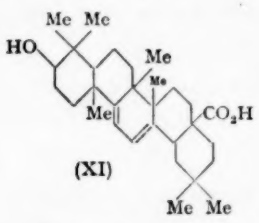
olean-10-enolic acid (V; R = H). With the object of deciding between the alternative formulæ (III; R = H) and (V; R = H), acetylketo*iso*oleanolic acid was re-examined.

Treatment of acetylketo-oleanolic lactone (II) with hydrogen bromide in ethanol, under the conditions described in the Experimental section, gave the hitherto undescribed keto*iso*oleanolic acid and not the acetyl derivative. Acetylation of this acid gave acetylketo*iso*oleanolic acid, the physical constants of which are in good agreement with those observed by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) for the product obtained directly from the alcoholic hydrogen bromide reaction mixture. The specific rotation (+47°) of the acetylketo*iso*oleanolic acid obtained by Kitasato (*loc. cit.*) by treatment of acetylketo-oleanolic lactone with hydrogen bromide in acetic acid is in good agreement with the value observed by us for keto*iso*oleanolic acid (+45°) but markedly different from that of the acetylketo*iso*oleanolic acid obtained by us (+61°) and by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) (+61°). Esterification of acetylketo*iso*oleanolic acid with diazomethane gave methyl acetylketo*iso*oleanolate. Since a direct comparison of the methyl acetylketo*iso*oleanolate obtained by bromination of methyl acetyldihydroketo-oleanolate with that obtained by the action of hydrogen bromide on acetylketo-oleanolic lactone was not made by Picard, Sharples, and Spring (*loc. cit.*), the possibility existed that the two materials, although similar, are distinct, the ester obtained by the bromination route being methyl 12-keto-olean-10-enolate (V; R = Me), and that obtained from acetylketo-oleanolic lactone (II) the isomeric methyl 12-keto-olean-13(18)-enolate (III; R = Me). We have now proved the identity by a direct comparison and confirmed it by hydrolysis

of methyl acetylketo*iso*oleanolate, obtained by the bromination route, to methyl keto*iso*-oleanolate identical with a specimen obtained by methylation of keto*iso*oleanolic acid:

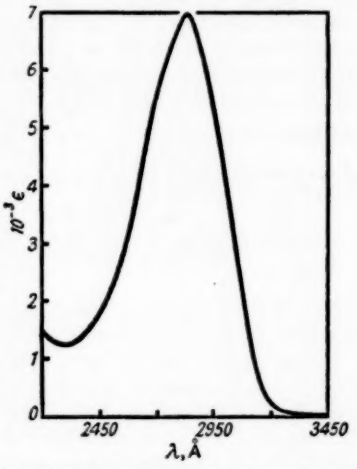
	From (IV):		From (II):	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
Methyl acetylketo*iso*oleanolate	208—209°	+57°	207—208°	+56°
Methyl keto*iso*oleanolate	233	+42	232—233	+40

Reduction of keto*iso*oleanolic acid with sodium amalgam gives a hydroxy-dienoic acid which is almost certainly identical with the dehydro*iso*oleanolic acid obtained by a similar reduction of acetylketo*iso*oleanolic acid by Kitasato (*loc. cit.*). The hydroxy-dienoic acid exhibits an intense light-absorption maximum (Fig.) at 2830 Å, which shows that the acid is olean-10 : 12-dienolic acid (XI) and consequently that acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-10-enolic acid (V; R = H) and not acetyl-12-keto-olean-13(18)-enolic acid (III; R = H). Acetylketo*iso*oleanolic acid sublimes unchanged in a vacuum at 250°. This pronounced stability to heat is in accord with formula (V; R = H) but not with formula (III; R = H); the $\beta\gamma$-unsaturated acid (III; R = H) would be expected to lose carbon dioxide when heated, to give the nor-β-amyrenonyl acetate (VI).



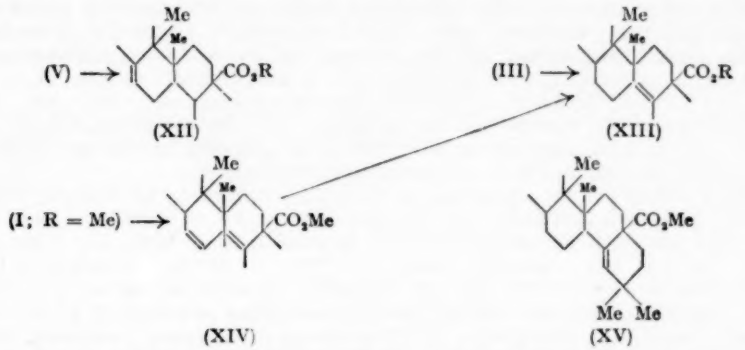
(XI)

The formation of an isomeric lactone from acetyl keto*iso*oleanolic acid by treatment with quinoline requires comment. We have made several attempts to prepare this lactone, the majority of which were unsuccessful. In one case, however, a very small yield of a neutral product was obtained, the melting point and crystalline form of which were similar to those observed by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*). Although this neutral compound was not available in sufficient quantity for a detailed study, it exhibits a light-absorption maximum at 2570 Å (ε = 14 000) and does not give a colour with tetranitromethane in chloroform. Whatever the nature of this neutral product, the presence therein of a strongly absorbing chromophore shows that it has not been produced from acetylketo*iso*oleanolic acid by simple additive interaction of carboxyl group and double bond, and its formation does not indicate a necessarily close proximity of these two functions in acetylketo*iso*oleanolic acid.



The preferred formula (V; R = H) for acetylketo*iso*oleanolic acid has been confirmed by an independent method. Clemmensen reduction of acetylketo*iso*oleanolic acid gives acetyl*iso*oleanolic acid (Ruzicka, Cohen, Furter, and Sluys-Veer, *loc. cit.*). Analogously, reduction of *iso*-β-amyrenonyl acetate (IX) by the Clemmensen method (Budziarek, Johnston, Manson, and Spring, *loc. cit.*) or by catalytic means (Jeger and Ruzicka, *Helv. Chim. Acta*, 1945, **28**, 209) gives 2-acetoxyolean-10-ene (X). If acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-10-enolic acid (V; R = H), acetyl*iso*oleanolic acid is acetylolean-10-enolic acid (XII; R = H). If, on the other hand, acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-13(18)-enolic acid (III; R = H), acetyl*iso*oleanolic acid will be acetylolean-13(18)-enolic acid (XIII; R = H), a formulation used without title in Elsevier's "Encyclopædia of Organic Chemistry" (1940, Vol. XIV, p. 543). The last formula assumes not only that (III; R = H) is a valid representation of acetylketo*iso*-oleanolic acid but that Clemmensen reduction of the αβ-unsaturated keto-acid has proceeded without migration of the double bond. Support for this last assumption is to be found in the stability of δ-amyrin acetate [2-acetoxyolean-13(18)-ene] to mineral acid (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236). Methyl acetylolean-13(18)-enolate

(methyl δ-acetyloleanolate) (XIII; R = Me) has been prepared by an unambiguous method from methyl acetyloleanolate (I; R = Me) by oxidation with selenium dioxide to methyl acetylolean-11 : 13(18)-dienolate (XIV) followed by catalytic reduction of the latter (Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532; Barton and Brooks,



J., 1951, 257). We find that catalytic reduction of methyl acetylketo*iso*oleanolate gives methyl acetyl*iso*oleanolate which differs from methyl δ-acetyloleanolate [methyl acetyloleanolate-13(18)-enolate] (XIII; R = Me), thus proving that acetylketo*iso*oleanolic acid is not acetyl-12-keto-olean-13(18)-enolic acid (III; R = H). We conclude that methyl acetyl*iso*oleanolate is methyl acetylolean-10-enolate (XII; R = Me) and that it is a third double-bond isomer of methyl acetyloleanolate (methyl acetylolean-12-enolate) (I; R = Me), the other two being methyl acetylmorolate (methyl acetylolean-18-enolate) (XV) (Barton and Brooks, *loc. cit.*) and methyl δ-acetyloleanolate [methyl acetylolean-13(18)-enolate] (XIII; R = Me).

Experimental

M. p.s are corrected, and rotations were measured in chloroform at room temperature in a 1-dm. tube.

Treatment of Acetylketo-oleanolic Lactone with Hydrogen Bromide.—The lactone (1 g.) in ethanol (50 c.c.) was saturated with dry hydrogen bromide, and the solution refluxed for 30 minutes. The mixture was again saturated with hydrogen bromide and refluxed for 30 minutes. After cooling to room temperature the mixture was saturated with hydrogen bromide, kept overnight, and then diluted with water. The mixture was extracted with ether, the extract washed with 3% aqueous sodium hydroxide, and the alkaline solution washed with ether before acidification with dilute hydrochloric acid. The precipitated solid was collected by means of ether, and the ethereal solution washed with water, dried ($MgSO_4$), and evaporated. The solid residue (0·8 g.) was crystallised from methanol–chloroform, to give *12-keto-olean-10-enolic acid* as prisms, m. p. 320° (decomp.), $[\alpha]_D$ +45° (*c*, 1·14) (Found: C, 76·8; H, 10·2. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·9%). Light absorption in ethanol: Max. at 2490 Å, ε = 10 000.

Methyl 12-keto-olean-10-enolate was obtained by esterification of the acid with ethereal diazomethane. The neutral product separated from methanol–chloroform as fine needles, m. p. 232—233°, $[\alpha]_D$ +40° (*c*, 0·53) (Found: C, 77·0; H, 10·2. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 10·0%). Light absorption in ethanol: Max. at 2500 Å, ε = 10 900. Kitasato (*Acta Phytochim.*, 1936, **9**, 43) gives m. p. 216°, $[\alpha]_D$ +25·7°, for this ester.

Acetyl-12-keto-olean-10-enolic acid was obtained by acetylation of 12-keto-olean-10-enolic acid with acetic anhydride in pyridine. Crystallisation of the product from methanol–chloroform gave the acetate as prisms, m. p. 328° (decomp.), $[\alpha]_D$ +61° (*c*, 1·00) (Found: C, 74·6; H, 9·7. Calc. for $C_{32}H_{48}O_5$: C, 74·9; H, 9·5%). Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) give m. p. 328—330°, $[\alpha]_D$ +61°, and Kitasato (*loc. cit.*) gives m. p. 324—330°, $[\alpha]_D$ +46·6°, for the acetyl-acid.

Methyl acetyl-12-keto-olean-10-enolate was obtained by acetylation of methyl 12-keto-olean-10-enolate with pyridine and acetic anhydride. It separated from methanol as plates, m. p.

207—208°, $[\alpha]_D$ +56° (*c*, 0·88) (Found: C, 75·5; H, 9·7. Calc. for $C_{33}H_{50}O_5$: C, 75·2; H, 9·6%).

Bromination of Methyl Acetyldihydroketo-oleanolate.—Methyl acetyldihydroketo-oleanolate (13 g.) in acetic acid (850 c.c.) was treated with a few drops of 48% aqueous hydrobromic acid, and then with a solution of bromine in acetic acid (5%; 85·5 c.c.) at 40°. The solution was kept at room temperature overnight before being heated on the steam-bath for 30 minutes. The solution was then poured into water, and the precipitated solid collected, washed with water, dried *in vacuo*, and crystallised from methanol, to give methyl acetyl-12-keto-olean-10-enolate (8·5 g.) as plates, m. p. 208—209°, $[\alpha]_D$ +57° (*c*, 1·06) (Found: C, 75·2; H, 9·7. Calc. for $C_{33}H_{50}O_5$: C, 75·2; H, 9·6%). A mixture with the specimen (m. p. 207—208°) obtained from acetylketo-oleanolic lactone had m. p. 207·5—209°. Methyl acetyl-12-keto-olean-10-enolate crystallises from methanol as either plates or prismatic needles according to the concentration of the solution, the two forms being interchangeable.

Hydrolysis of methyl acetyl-12-keto-olean-10-enolate, obtained by the bromine route, with % ethanolic potassium hydroxide for 2 hours followed by crystallisation from aqueous methanol gave methyl 12-keto-olean-10-enolate as needles, m. p. 233°, $[\alpha]_D$ +42° (*c*, 0·95) (Found: C, 77·1; H, 10·1. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 10·0%). A mixture of the ester with the hydroxy-ester (m. p. 232—233°) from acetylketo-oleanolic lactone had m. p. 233°.

Methyl Acetylolean-10-enolate.—Methyl acetyl-12-keto-olean-10-enolate (1 g.) in stabilised glacial acetic acid (75 c.c.) was shaken with hydrogen in the presence of platinum (0·4 g.) at room temperature and atmospheric pressure for 2 days, during which the equivalent of approx. 2 mols. of hydrogen was absorbed. The solution was filtered, the filtrate diluted with water, and the crystalline solid, m. p. 172—177°, separating collected. After two recrystallisations from methanol–chloroform the product had m. p. 172—177° and showed an absorption maximum in ethanol at 2830 Å (ε = 880). The solid (0·47 g.) was dissolved in light petroleum (b. p. 60—80°; 100 c.c.) and chromatographed on activated alumina (Grade II; 15 × 2 cm.). Light petroleum (b. p. 40—60°; 620 c.c.) and light petroleum–benzene (4 : 1; 100 c.c.) eluted a solid (235 mg.), m. p. 184—187°, crystallisation of which from methanol–chloroform gave *methyl acetylolean-10-enolate* as needles, m. p. 191·5—192·5°, $[\alpha]_D$ +52°, +52° (*c*, 0·84; 0·40) (Found: C, 77·4; H, 10·4. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). Methyl acetylolean-10-enolate gives a yellow colour with tetranitromethane in chloroform; it does not show selective absorption in the ultra-violet region.

After the column had been washed with light petroleum–benzene (4 : 1; 500 c.c.), benzene (200 c.c.) eluted a solid (42 mg.), m. p. 191—196°, $\lambda_{max.}$ 2830 Å ($\varepsilon \simeq 1500$). This fraction was not obtained pure but probably contained an appreciable quantity of methyl acetylolean-10 : 12-dienolate.

Methyl olean-10-enolate was obtained by treatment of methyl acetylolean-10-enolate (100 mg.) with boiling ethanolic potassium hydroxide (5%; 10 c.c.) for 2 hours. Crystallisation of the product from methanol–chloroform yielded the ester as needles, m. p. 213—214°, $[\alpha]_D$ +41° (*c*, 0·93) (Found: C, 79·1; H, 11·0. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%).

Treatment of Acetyl-12-keto-olean-10-enolic Acid with Quinoline.—Acetyl-12-keto-olean-10-enolic acid (0·30 g.) in quinoline (50 c.c.) was heated for 2 hours at 250—255°. The solution was poured into dilute hydrochloric acid (7%; 250 c.c.), and the mixture extracted with ether. The ethereal extract was washed successively with dilute hydrochloric acid, sodium hydroxide solution, and water, and dried ($MgSO_4$). Removal of the solvent gave a dark brown residue (46 mg.), which after being washed with a little methanol was crystallised from methanol, yielding needles, m. p. 278—281°; a mixture with acetylketo-oleanolic lactone (m. p. 280—282°) had m. p. 262—270°. Light absorption in ethanol: Max. at 2570 Å, ε = 14 200.

Acidification of the alkaline washings of the ethereal extract, followed by crystallisation of the product from methanol–chloroform, gave acetyl-12-keto-olean-10-enolic acid (0·24 g.) as prisms, m. p. 316—319° (decomp.).

Olean-10 : 12-dienolic Acid.—12-Keto-olean-10-enolic acid (1·2 g.) was heated under reflux in ethanol (90%; 100 c.c.) with sodium amalgam (3%; 70 g.) for 3 hours. The cold mixture was filtered, then acidified with dilute hydrochloric acid, and the precipitated solid extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallised from methanol, to give olean-10 : 12-dienolic acid as prisms, m. p. 293—295°, $[\alpha]_D$ +202° (*c*, 0·78) (Found: C, 79·2; H, 10·2. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). Light absorption in ethanol: Max. at 2830 Å, ε = 7000. Kitasato (*loc. cit.*) gives m. p. 295—300°, $[\alpha]_D$ +206·8°, for the sodium amalgam reduction product from acetylketo*iso*oleanolic acid. Purification of the acid was extremely difficult and, although the m. p. remained unaltered

after each crystallisation, the specific rotation and the intensity of the ultra-violet absorption maximum increased slightly; lack of material did not permit the crystallisations to be continued until constant values were obtained. Both values are probably somewhat low, a comment which likewise applies to those for the methyl ester.

Methyl olean-10 : 12-dienolate was obtained by esterification of the acid with ethereal diazomethane. It separates from methanol as needles, m. p. 194—196°, $[\alpha]_D$ +203° (*c*, 0·92). Light absorption in ethanol: Max. at 2840 Å, $\varepsilon = 6800$. Kitasato (*loc. cit.*) gives m. p. 198° for the methyl ester of the acid obtained by sodium amalgam reduction of acetylketo*iso*oleanolic acid.

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85. *Nucleophilic Displacement Reactions in Aromatic Systems. Part I. Kinetics of the Reactions of Chloronitropyridines with Aromatic Amines and with Pyridine.*

By R. R. BISHOP, E. A. S. CAVELL, and N. B. CHAPMAN.

The Arrhenius parameters for the reactions between 2-chloro-5-nitro- and 2-chloro-3-nitro-pyridine and primary aromatic amines have been determined. Also the reactions of the same compounds and those of 4-chloro-3-nitropyridine and of chloro-2 : 4-dinitrobenzene with pyridine have been studied, and Arrhenius parameters evaluated.

The reactions of pyridine, despite its rather greater "nucleophilic power," are significantly slower than those of aniline. This is ascribed to the retarding effect of steric hindrance with pyridine and, more tentatively, to a stabilisation of the transition state by interaction of amino-hydrogen with the oxygen of an *o*-nitro-group, and to increased solvation of the transition state for primary amines.

The observed magnitudes of the Arrhenius parameters for the different reactions are correlated with the structures of the halogeno-compounds, with special reference to steric and polar factors. The influence of nitro-groups and cyclic nitrogen atoms on the mobility of the halogens is elucidated.

DURING the last fifty years, the kinetics of the nucleophilic displacement of halogen atoms from aromatic carbon atoms in appropriately substituted halogenobenzenes have received considerable attention, and such investigations are in progress at present. When, however, the aromatic carbon atom forms part of a heterocyclic system, our knowledge of the kinetics of these displacement reactions is extremely scanty. The immediate object of the present studies is to remedy this situation, for the subject has considerable intrinsic interest: the ultimate object is to contribute to the theoretical organic chemistry of heterocyclic compounds, particularly of the pyrimidine series, to which many biologically important compounds belong. Lack of quantitative results concerning the reactions of halogen derivatives of even the simplest heterocyclic compounds makes it necessary first to clear the ground by investigations of pyridine derivatives analogous to 2- and 4-halogeno-pyrimidines.

It is commonly asserted (*e.g.*, by Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford Univ. Press, 1937, p. 523) that in aromatic systems the cyclic nitrogen atom and the substituent nitro-group cause similar disturbances of the aromatic electron cloud. The present communication records kinetic studies which lead to a quantitative

comparison of these effects in terms of the velocity coefficients and Arrhenius parameters of analogous reactions in the pyridine and the benzene series. We are at present also studying the pyrimidine series in similar fashion and filling in certain gaps in our knowledge of the benzene series. This problem has been approached from a different and more fundamental viewpoint by quantum-mechanical methods, mainly the molecular-orbital approximation (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900; Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87).

Of benzenoid compounds which undergo nucleophilic displacement reactions, chloro-2 : 4-dinitrobenzene has been studied most, and the kinetics of many of its reactions have been examined in detail (Brady and Cropper, *J.*, 1950, 507; Blanksma and Schreinemachers, *Rec. Trav. chim.*, 1933, **52**, 428; van Opstall, *ibid.*, p. 901; Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669; *J.*, 1935, 1410). We have therefore chosen analogous pyridine derivatives for our own studies, *viz.*, 2-chloro-5-nitropyridine, which had previously been investigated in a semi-quantitative way by Mangini and Frenguelli (*Gazzetta*, 1943, **73**, 313), and 4-chloro-3-nitropyridine. These compounds also are analogous to 2- and 4-halogenopyrimidines. Halogenonitropyridines are preferable to simple halogenopyridines because they react at speeds conveniently more rapid for kinetic work. Moreover, there is much less information available about the reactions of the benzenoid compounds analogous to halogenopyridines, *viz.*, halogenomononitrobenzenes. We have also included 2-chloro-3-nitropyridine despite the fact that information about the reactions of the analogous but inaccessible chloro-2 : 6-dinitrobenzene is scanty, to complete the series. We chose primary aromatic amines as our nucleophilic reagents in the first place, because they have been widely studied with chloro-2 : 4-dinitrobenzene (Singh and Peacock, *loc. cit.*, van Opstall, *loc. cit.*).

There is some evidence (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127) that reactions of halogenated heterocyclic compounds of the type under review are subject to acid-catalysis under appropriate conditions: we shall present evidence that conditions can be found in which such catalysis is negligible. Also we shall note an example of it. Morley and Simpson (*J.*, 1949, 1014) have provided preparative evidence in support of Banks's views. However, this possibility led us to study one reaction for each halogeno-compound in which no acid is generated during the reaction. Primary amines generate acid (*e.g.*, anilinium ions) during reaction; tertiary amines, however, do not, and we have therefore studied the reactions of pyridine. Whereas the acid-generating reactions should, on Banks's hypothesis, be autocatalytic, those of pyridine and other tertiary amines should be free from this complexity. Very interesting results emerged, so we are at present extending our studies to include other *cyclic* tertiary amines, the reactions of which appear simpler than those of primary amines. We have also examined the reaction of chloro-2 : 4-dinitrobenzene with pyridine for comparison.

4-Chloro-3-nitropyridine presents special difficulties because it is very reactive. It shows a slow but definite reaction with the ethanol used as solvent, and a measurable self-reaction, both of which liberate chloride ion, and its reactions with primary amines appear to be strongly autocatalytic, possibly because of the acid-catalysis discovered by Banks (*loc. cit.*). However, we have been able to study the kinetics of its reactions with pyridine, which are quite regular at low temperatures, and we propose further studies with this compound in other solvents in which it may be possible to eliminate unwanted side reactions.

Previous kinetic studies with the most closely analogous benzenoid compounds, halogeno-2 : 4-dinitrobenzenes, have focused attention on the influence either of the structure of the amine on the reactions (Singh and Peacock, *loc. cit.*) or of variation of the halogen in the halogeno-compound. We shall return to the former problem in the discussion and one of us has discussed the other problem elsewhere (Chapman and Parker, *J.*, 1951, 3301). The influence of a nuclear methyl group in chloro-2 : 4-dinitrobenzene on reactions with aniline has also been investigated incompletely by Lindemann and Pabst (*Annalen*, 1928, **462**, 24). Their views have proved of interest in relation to the discussion which follows, but this is a problem which needs further investigation before much progress can be made, to which subject we hope to give attention in due course.

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

Materials.—Chloro-compounds. Chloro-2 : 4-dinitrobenzene was distilled, b. p. 136°/0·2 mm., and the middle fraction was crystallised from ethanol; it had m. p. 51°. 2-Chloro-5-nitropyridine, m. p. 108° (for preparation cf. Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1941, **64**, 1696, and Phillips, *J.*, 1941, 12), was crystallised from methanol. 2-Chloro-3-nitropyridine, m. p. 102°, was prepared by the action of phosphorus pentachloride and phosphoryl chloride on 2-hydroxy-3-nitropyridine, and crystallised from methanol with charcoal.

2-Hydroxy-3-nitropyridine was prepared by a method based on that of Binz and Maier-Bode (*Angew. Chem.*, 1936, **49**, 486). The liquor obtained by deamination with nitrous acid of 2-aminopyridine was heated to boiling, then cooled somewhat, and excess of sodium hydroxide pellets added with stirring until sodium sulphate remained undissolved in the hot liquid. After cooling the solid product was filtered off, and boiled with at least two 500-ml. portions of ethanol. After filtration of the hot liquor, it was cooled to 10° and an equal volume of ether added, which completed the separation of the hydrated sodium salt ($C_5H_4N{\cdot}ONa,2H_2O$) of 2-hydroxypyridine, as shining white leaflets, which on being dried at 100° gave the anhydrous salt. The anhydrous sodium salt was nitrated directly with a cold mixture of fuming nitric acid (*d* 1·52) and concentrated sulphuric acid. The product was poured on crushed ice, and the yellow solid which was precipitated was filtered off. A further small amount was obtained by making the filtrate neutral to methyl-orange with concentrated aqueous sodium hydroxide. The combined solids were boiled three times with about 1 l. of methanol. From the resulting solutions, after filtration hot, reasonably pure 2-hydroxy-3-nitropyridine separated, of m. p. 215—217°, and was used for further work. There is no advantage in liberating the pyridone from its salt for nitration.

1-4′-Pyridylpyridinium chloride hydrochloride was prepared by Koenigs and Greiner's method (*Ber.*, 1931, **64**, 1052), using pure dry pyridine and redistilled thionyl chloride. The product, after being washed with ethanol, was a pale yellow powder, m. p. 150—151°, whence 4-hydroxypyridine, isolated as nitrate, m. p. 189—191°, was obtained by heating it with water at 150° for 8 hours in a stainless-steel autoclave (Koenigs and Greiner, *loc. cit.*). The nitrate was converted into 4-hydroxy-3-nitropyridine by nitration with fuming nitric acid (*d* 1·52) in concentrated sulphuric acid (cf. Koenigs and Fulde, *Ber.*, 1927, **60**, 2107, and Crowe, *J.*, 1925, 2028) (Found : N, 20·6. Calc. for $C_5H_4O_3N_2$: N, 20·1%). We find Crowe's method superior, using concentrated and not fuming sulphuric acid as recommended by Koenigs *et al.*; also we find 20 hours' heating on the water-bath sufficient. The method of Koenigs *et al.* gives products difficult to free from dinitro-compounds.

4-Chloro-3-nitropyridine was prepared by a method based on that of Reitmann (*Chemistry and Medicine*, 1934, **2**, 384), who obtained it in a relatively impure state. We find the following procedure, especially the final crystallisation, quite essential to obtaining a pure product. Phosphorus pentachloride (16 g., 0·077 mol.) was covered with phosphoryl chloride and heated to 60°. 4-Hydroxy-3-nitropyridine (10 g., 0·071 mol.) was gradually added, and after the whole had been kept on the warm water-bath for several hours, the phosphoryl chloride was distilled at 15 mm. The residue was treated with ice-water and covered with a layer of ether, and aqueous sodium carbonate added to faint alkalinity to methyl-orange. The ethereal layer was separated, the aqueous layer re-extracted with ether, the ethereal solution dried ($CaCl_2$), the ether removed, and the 4-chloro-3-nitropyridine distilled (b. p. 68—70°/0·5 mm.), forming colourless crystals, m. p. 34°, by crystallisation from sodium-dried ether [Found : C, 37·6; H, 1·6; N, 17·1; Cl (Stepanow), 22·5. Calc. for $C_5H_3O_2N_2Cl$: C, 37·85; H, 1·9; N, 17·65; Cl, 22·4%). The compound must be stored in the cold in a dry atmosphere and liberates chloride ion on brief heating at 100°.

Amines. Aniline, *m*-toluidine, and *p*-phenetidine were purified through their acetyl derivatives, followed by fractionation of the regenerated amine under reduced pressure. *p*-Toluidine (pure commercial) was repeatedly recrystallised from light petroleum (b. p. 40—60°) until it melted sharply at 45°. *p*-Anisidine was treated with charcoal in boiling ethanol, the ethanol removed, and the residue twice recrystallised from light petroleum (b. p. 40—60°)–benzene (4 : 1), and had m. p. 59°. Pyridine (May and Baker, pure) was dried (BaO) and fractionated through a 20-in. Fenske column, a fraction of b. p. 115° being collected; it was also further purified through the pure perchlorate, m. p. 290·5—291°. Small, but definite, differences in reaction rate were observed for the two samples. The results which follow are

for perchlorate-purified pyridine since the reaction liquid darkens considerably with pyridine that has only been redistilled.

Products.—The following products of the reactions studied have not previously been described:

3-*Nitro*-2-p-*toluidinopyridine*, prepared by heating 2-chloro-3-nitropyridine (1 g.) and *p*-toluidine (1 g.) in ethanol (5 c.c.) under reflux for 6 hours, m. p. 73° (red needles) (Found: C, 63·4; H, 4·8; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%).

2-*Anilino*-3-*nitropyridine*, m. p. 75° (orange-red needles), similarly prepared (Found: C, 61·6; H, 4·2; N, 19·2. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2; N, 19·5%).

3-*Nitro*-4-p-*toluidinopyridine*, m. p. 123° (bright yellow needles), similarly obtained from 4-chloro-3-nitropyridine (Found: C, 62·5; H, 4·7; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%).

The quaternary chlorides obtained from the chloronitropyridines were prepared in the above way, but were difficult to purify and always had low chlorine analyses. They were therefore converted into the corresponding picrates which could be isolated pure:

1-(5-*Nitro*-2-*pyridyl*)*pyridinium picrate*, yellow needles (from methanol), m. p. 181·5° (Found: C, 44·9; H, 2·5; N, 20·2. $C_{16}H_{10}O_9N_6$ requires C, 44·7; H, 2·3; N, 19·5%).

1-(3-*Nitro*-2-*pyridyl*)*pyridinium picrate*, yellow needles (from methanol), m. p. 103° (Found: C, 44·7; H, 2·4; N, 19·4%).

1-(3-*Nitro*-4-*pyridyl*)*pyridinium chloride*, white crystals, m. p. 160—161° (decomp.) (Found: N, 17·3; Cl, 14·6%). $C_{10}H_7O_2N_3Cl$ requires: N, 17·7; Cl, 14·9%).

Solvent.—Commercial absolute ethanol was dried by Lund and Bjerrum's method (*Ber.*, 1931, **64**, 210) and fractionated. Its water content was determined by the Karl Fischer reagent (*Angew. Chem.*, 1935, **48**, 394) and then adjusted to 99·8% (by wt.) by addition of water.

Procedure.—This was similar to that of Singh and Peacock (*J. Phys. Chem.*, 1936, **40**, 669) and of Rheinlander (*J.*, 1923, **123**, 3099). 100 C.c. of a solution, 0·1M. with respect to the chloro-compound and 0·4M. with respect to the amine, were prepared at thermostat temperature. Aliquots were withdrawn at intervals and the solution run into a mixture of 0·05N-silver nitrate and dilute nitric acid, covered with benzene. This process arrests the reaction, fixes the chloride ion formed, and eliminates organic halogen compounds from the aqueous ethanolic layer. The benzene layer was washed twice with water, and the residual silver nitrate determined by the Volhard method; hence the concentration of chloride ion produced could be calculated. In the reaction with *p*-anisidine and *p*-phenetidine the Volhard method could not be used since the ferric iron indicator oxidised the amines giving deeply coloured solutions. In these cases chloride ion was determined gravimetrically. Some of the reactions were also studied by the method of sealed bulbs.

2-Chloro-5-nitro- and 2-chloro-3-nitro-pyridine are quite unaffected by boiling ethanol. 4-Chloro-3-nitropyridine, however, slowly liberates chloride ion in 0·1M-ethanolic solution at 30°, by either solvolysis or self-reaction. This is negligible during the first 200 minutes of the reaction. After 1000 minutes, however, some 45% of the compound has reacted, and the reaction is virtually complete after about 3000 minutes. These results suggest that the reaction is autocatalytic by virtue of the hydrochloric acid liberated by solvolysis. However, in the presence of a three-fold excess of pyridine, no autocatalysis was observed. It appears that under these conditions the predominating reaction is that between the amine and the halogeno-compound. For the reaction of 4-chloro-3-nitropyridine with pyridine at 30°, there is no observable catalysis up to 50% decomposition (cf. p. 441).

Results

Detailed values are given for some of the reactions of each chloro-compound, and all the results are summarised in Table 2. Since the chloro-compounds consume two moles of primary amine per mole,

$$dx/dt = k(a - 2x)(b - x)$$

whence
$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

For tertiary amines

$$dx/dt = k(a - x)(b - x)$$

whence
$$k = \frac{1}{t(a - b)} 2{\cdot}303 \log_{10} \frac{b}{a} \cdot \frac{a - x}{b - x}$$

Evidence of order of reaction is given in selected cases. The experimentally observed times are recorded in minutes but the velocity coefficients are given in terms of the more usual units, *viz.*, l. mol.$^{-1}$ sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures are accurate to $\pm 0{\cdot}03°$.

TABLE 1.

Reactions of 2-chloro-5-nitropyridine.

Aniline at 55·0°.

Time (min.)	301	1047	1417	1441	2500	2565
Decompn., %	7·6	24·5	30·3	30·5	46·6	47·7
$k \times 10^5$	11·71	12·08	11·69	11·61	12·10	12·33

Mean $k = 11{\cdot}9 \pm 0{\cdot}2 \times 10^{-5}$.

p-*Toluidine at* 55·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	150	350	500	600	700	800	920	1160
Decompn., %	11·0	23·4	31·4	35·6	40·4	44·1	47·8	55·8
$k \times 10^5$	33·0	34·0	34·3	34·2	34·8	34·7	34·2	35·2

Mean $k = 34{\cdot}3 \pm 0{\cdot}4 \times 10^{-5}$; 50% decompn. at 989 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 35{\cdot}9 \pm 0{\cdot}1 \times 10^{-5}$; 50% decompn. at 1883 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}90$. Ratio of concns. = 2·00.

p-*Anisidine at* 45·0°.

Time (min.)	121·5	250·5	404	470	619
Decompn., %	15·0	28·8	40·7	44·1	58·2
$k \times 10^5$	58·2	60·15	60·1	58·7	59·3

Mean $k = 59{\cdot}3 \pm 0{\cdot}6 \times 10^{-5}$.

Pyridine at 60·0°.

(*a*) Amine 0·4015M., chloro-compound 0·0994M.

Time (min.)	1630	2850	4500	7020	8600	10 400	12 900	16 040
Decompn., %	11·6	17·5	27·2	38·6	45·0	50·6	59·1	66·3
$k \times 10^5$	3·05	(2·60)	2·85	3·02	3·05	3·02	3·13	3·13

Mean $k = 3{\cdot}04 \pm 0{\cdot}06 \times 10^{-5}$; 50% decompn. at 10 180 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 2{\cdot}93 \pm 0{\cdot}04 \times 10^{-5}$; 50% decompn. at 21 210 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}08$. Effective ratio of concns. = 2·01.

Reactions of 2-chloro-3-nitropyridine.

p-*Toluidine at* 45·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	245	370	513	651	824	1056	1229	1702
Decompn., %	13·2	18·9	25·5	30·3	36·6	42·9	47·3	57·0
$k \times 10^5$	24·8	24·8	25·5	25·2	25·5	25·2	25·2	24·7

Mean $k = 25{\cdot}1 \pm 0{\cdot}25 \times 10^{-5}$; 50% decompn. at 1352 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 24{\cdot}2 \pm 0{\cdot}25 \times 10^{-5}$; 50% decompn. at 2800 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}07$. Ratio of concns. = 2·00.

Pyridine at 60·0°.

(*a*) Amine 0·3996M., chloro-compound 0·0986M.

Time (min.)	2800	5800	8900	12 860	17 230	21 600
Decompn., %	10·9	20·2	28·8	38·6	47·9	56·0
$k \times 10^5$	1·68	1·64	1·64	1·67	1·68	1·69

Mean $k_2 = 1{\cdot}66 \pm 0{\cdot}02 \times 10^{-5}$; 50% decompn. at 18 730 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 1{\cdot}61 \pm 0{\cdot}04 \times 10^{-5}$; 50% decompn. at 36 560 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}95$. Effective ratio of concns. = 1·99.

Reactions of 4-chloro-3-nitropyridine.

Pyridine at 30·0°.

(*a*) Amine 0·400M., chloro-compound 0·100M.

Time (min.)	2320	3800	5600	6800	9860	14 200
Decompn., %	15·9	25·0	34·6	40·2	51·8	65·4
$k \times 10^5$	3·30	3·40	3·47	3·48	3·50	3·67

Mean $k = 3{\cdot}47 \pm 0{\cdot}08 \times 10^{-5}$; 50% decompn. at 8999 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: 50% decompn. at 18 530 min. $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}06$. Ratio of concns. = 2·00.

TABLE 1—*continued.*

Reactions of chloro-2 : 4-dinitrobenzene.

Pyridine at 60·0°.

(*a*) Amine 0·3996M., chloro-compound 0·100M.

Time (min.)	311	520	615	750	1010	1075	1317	2570
Decompn., %	11·5	18·6	21·2	25·3	31·2	32·2	37·5	58·6
$k \times 10^6$	15·9	16·6	16·3	16·5	16·1	15·8	15·7	15·3

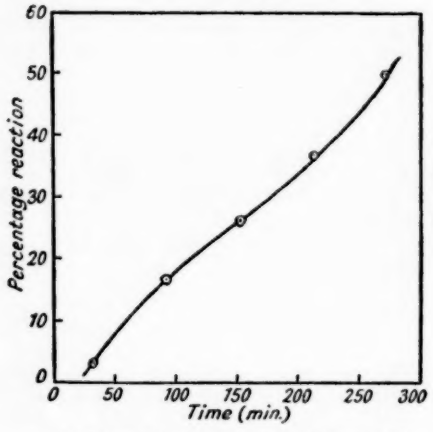
Mean $k = 16·0 \pm 0·4 \times 10^{-6}$; 50% decompn. at 2113 min.

(*b*) Amine 0·200M., chloro-compound 0·0500M.: mean $k = 15·7 \pm 0·2 \times 10^{-6}$; 50% decompn. at 4304 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·04$. Ratio of concns. = 2·00.

DISCUSSION

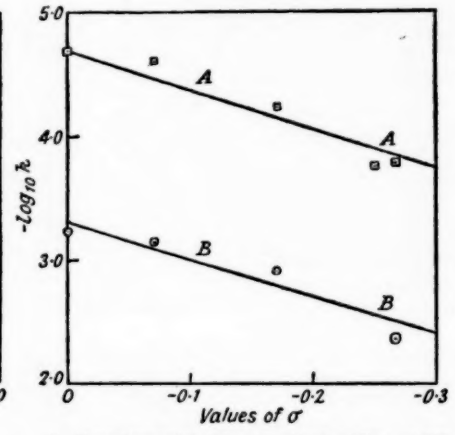
Banks's discovery (*loc. cit.*) of the acid-catalysis of nucleophilic displacement of halogen from halogenonitropyridines implies that the reactions of the primary amines should be autocatalytic, the amine cations formed constituting the acidic species. With the weaker acids—conjugate acids of stronger bases—the acid-catalysis is apparently negligible in the first half of the reactions of 2-chloro-5-nitro- and 2-chloro-3-nitro-pyridines. The

FIG. 1.



Reaction of 4-chloro-3-nitropyridine with aniline in ethanol at 20°.

FIG. 2.



A. Reactions of 2-chloro-5-nitropyridine at 65°.
B. Reactions of chloro-2 : 4-dinitrobenzene at 65°.

autocatalysis is observable, however, even under conditions unfavourable to it, with 4-chloro-3-nitropyridine, as Fig. 1 shows. For the most part the reactions under discussion obey a second-order rate law quite satisfactorily.

The reactions of chloro-2 : 4-dinitrobenzene with primary aromatic amines obey, to a fair degree of approximation, the Hammett ρ–σ relationship (Hammett, "Physical Organic Chemistry," New York, 1942, p. 184). The same relation holds also to much the same degree of accuracy for the reactions of 2-chloro-5-nitropyridine, as Fig. 2 shows. However it has not been possible, because of very unfavourable reaction rates, to cover a sufficiently large range of values of σ to obtain a ρ value of any great accuracy.

Influence of the Structure of the Amine on the Parameters of the Arrhenius Equation.—In its inception, the present work was not primarily concerned with the variations of the structure of the amine. The study of tertiary amines was undertaken in order to eliminate acid-catalysis entirely. Some results of Peacock *et al.* and the authors are collected in Table 3 to illustrate this aspect of the problem. For *primary* aromatic amines the influence of substituents in the base on the energy of activation, E, is in the order expected from their known "nucleophilic powers" as measured by their basic strengths (admittedly

TABLE 2.

Temp.	Amine	2-Chloro-5-nitropyridine (a)	2-Chloro-5-nitropyridine (b)	2-Chloro-3-nitropyridine (a)	2-Chloro-3-nitropyridine (b)	4-Chloro-3-nitropyridine (a)	4-Chloro-3-nitropyridine (b)	1-Chloro-2 : 4-dinitrobenzene (a)	1-Chloro-2 : 4-dinitrobenzene (b)
45·0°	Aniline	17·4—42·9	6·03—6·27	16·3—49·1	7·88—8·22				
45·0	*p*-Toluidine	9·2—61·8	16·5—17·8	13·2—56·9	24·7—25·5				
45·0	*p*-Anisidine	15·0—58·2	58·2—60·1						
50·0	Pyridine	1·5—29·4	1·25—1·32	12·5—25·2	0·648—0·678	12·4—75·9	1·41—1·52 *	21·7—40·2	7·20—7·62
55·0	Aniline	7·6—47·7	11·61—12·33	27·3—61·0	16·8—17·0				
55·0	*p*-Toluidine	11·0—55·8	33·0—35·2	18·6—48·8	49·3—50·1				
55·0	*p*-Anisidine	23·9—45·7	99·2—101·7						
60·0	Pyridine	11·6—66·3	2·85—3·13	10·9—56·0	1·64—1·69	9·1—60·3	3·53—3·80 *	11·5—58·6	15·3—16·6
65·0	Aniline	8·0—45·6	21·2—22·5	14·0—55·0	30·2—32·3				
65·0	*p*-Toluidine	15·4—53·4	55·8—59·7	16·8—52·2	91·3—94·0				
65·0	*p*-Anisidine	17·4—44·2	166·7—176·7						
70·0	Pyridine	13·5—56·3	6·70—7·03	11·5—60·3	3·53—3·72	21·2—86·8	8·95—9·75 *	15·9—53·5	32·7—33·8
65·0	*m*-Toluidine	32·7—48·3	24·7—26·2						
65·0	*p*-Phenetidine	25·3—52·0	171·7—185·0						

(*a*) Extreme values of percentage reaction. (*b*) Extreme values of $k \times 10^4$.
* Temp. 30° less. (For mean k's at 55° see Table 3.)

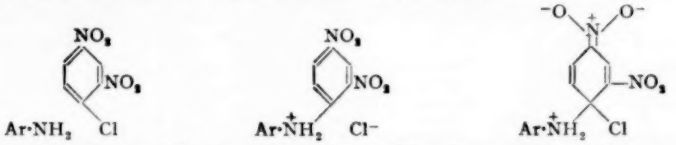
TABLE 3.

Reaction no.	Amine	Chloro-compound	$k^{55} \times 10^4$	E (cals.)	$\log_{10} A$
1	Aniline	Chloro-2 : 4-dinitrobenzene	353	11 200	4·0 [1]
2	*p*-Toluidine	,,	970	10 100	3·6 [1]
3	*p*-Anisidine	,,	2958	9 700	3·9 [1]
4	Pyridine	,,	11·1 ± 0·2	16 700	6·2
5	Aniline	2-Chloro-5-nitropyridine	11·9 ± 0·22	13 100	3·8
6	*p*-Toluidine	,,	34·3 ± 0·4	12 700	3·9
7	*p*-Anisidine	,,	101·2 ± 0·7	11 500	3·5
8	Pyridine	,,	1·97 ± 0·04	18 100	6·3
9	*m*-Toluidine	,,	25·0 ± 0·5 [2]	—	—
10	*p*-Phenetidine	,,	180 ± 5 [2]	—	—
11	Aniline	2-Chloro-3-nitropyridine	16·9 ± 0·1	14 500	5·0
12	*p*-Toluidine	,,	50·0 ± 0·6	13 900	4·9
13	Pyridine	,,	1·03 ± 0·015	18 700	6·3
14	Pyridine	4-Chloro-3-nitropyridine	32·1 ± 0·6	16 900	6·8

Units of A and k are l. mol.$^{-1}$ sec.$^{-1}$. Energies of activation are accurate to ± 300 cals., values of $\log_{10} A$ to ± 0·2 unit.
[1] Singh and Peacock, *loc. cit.* [2] At 65°.

a very rough measure of " nucleophilic power "). With pyridine, however, which may be regarded on the above basis as of greater " nucleophilic power " than aniline, the rate at which chloride ion is displaced from chloro-2 : 4-dinitrobenzene at 55° is *less* than that for aniline by a factor of ~30 because of a marked rise in E partly offset by an increase in the non-exponential term A (Table 3). Similar results are obtained with β- and γ-picolines (Cavell, unpublished). Also for the reactions of 2-chloro-5-nitropyridine and 2-chloro-3-nitropyridine qualitatively similar results are observed.

The transition state for the reaction between chloro-2 : 4-dinitrobenzene and aromatic amines may be represented as a hybrid of the following canonical forms :



The transition state for pyridine is very similar. The nitro-group written as $-NO_2$ has its usual structure. Now in picryl iodide the *o*-nitro-groups are almost perpendicular to the ring (Huse and Powell, *J.*, 1940, 1398) and geometrical considerations make it probable that in chloro-2 : 4-dinitrobenzene the *o*-nitro-group is inclined to the ring and not coplanar with it as is the *p*-nitro group. Experimental evidence is apparently unavailable. To the extent that the *o*-nitro-group is inclined to the ring up to 90°, its conjugation with the ring will be reduced, thus reducing its electromeric effect.

The observed difference in rate between the reactions in question (nos. 1 and 4, Table 3) is partly caused by steric hindrance, as inspection of appropriate models suggests. The probable geometry of the two analogous transition states is indicated in Figs. 3 and 4. Calculation of the steric compressions in each transition state, accepted bond distances and intervalency angles being used, according to the principles set forth by Dostrovsky,

FIG. 3.

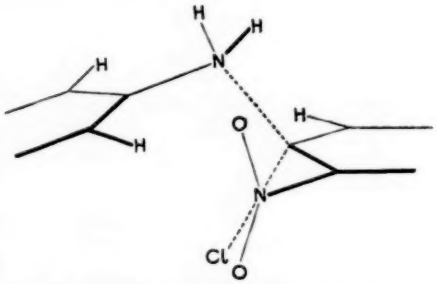
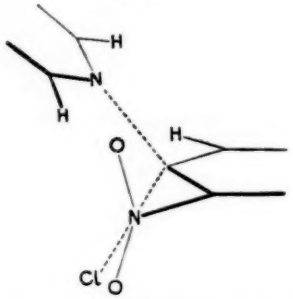
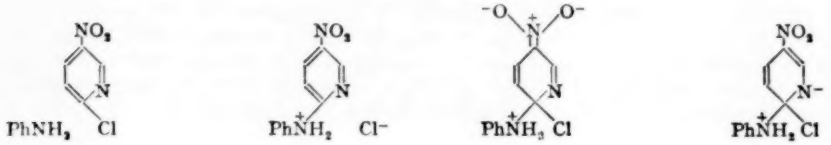


FIG. 4.

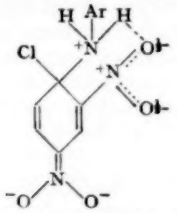


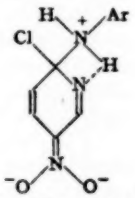
Hughes, and Ingold (*J.*, 1946, 173), confirms the view that the reaction of pyridine is more subject to steric hindrance than is that of aniline. Several assumptions are made in setting up the models of the transition states used, but the same assumptions are made in each case. Thus the *o*-nitro-group has been assumed to adopt the " perpendicular " configuration, for the sake of definiteness, and the C–N partial-bond distance has been set at 10% greater than the length of a single C–N bond (Glasstone, Laidler, and Eyring, " Theory of Rate Processes," New York, 1945, p. 151). The valency angles at the seat of substitution have been taken as tetrahedral. No attempt has been made to assess the compression energies involved, but only to arrive at a qualitative conclusion about the relative importance of steric hindrance in the two cases. Similar conclusions hold good for the reactions of 2-chloro-3-nitropyridine, where the geometrical essentials are virtually the same as with chloro-2 : 4-dinitrobenzene. However, with 2-chloro-5-nitropyridine, similar but smaller differences in rate are observed (Table 3), and in this case it is improbable that steric hindrance is significant, for the calculations suggest very strongly that the *o*-nitro-group is largely responsible for the steric compressions with the other halides. The transition state for the reactions with aniline may be represented thus :



Hence we must seek some other factor to account for the difference of Arrhenius parameters for the reactions of 2-chloro-5-nitropyridine with aniline and pyridine, with the probability that the same factor operates with 2-chloro-3-nitropyridine and chloro-2 : 4-dinitrobenzene. There is a possibility of a variable electrostatic contribution to the different energies of activation, arising from varying interactions between the dipoles of the reagents. For the present, we reserve judgment on this and we neglect it in what follows.

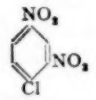
Comparison of reactions 5 and 8 (Table 3) suggests that some factor associated with amino-hydrogen plays an important part in the reaction of aniline. We propose as a tentative hypothesis that there is hydrogen-bond formation in the transition state, with a contribution to the hybrid from the following structures for the different reactions :

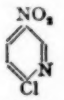




A similar idea has been advanced by Lindemann and Pabst (*loc. cit.*) without much evidence in its favour. Although there appears to be no experimental evidence for hydrogen-bond formation in 2-nitrodiphenylamines or 2-anilinopyridines, which might be expected if our hypothesis were true, there is spectroscopic evidence of hydrogen-bond formation in 1-amino-2-nitro- and 2-amino-1-nitro-naphthalene (Hathway and Flett, *Trans. Faraday Soc.*, 1949, **45**, 818), which possess analogous structures. The geometry of the two transition states is compatible with this hypothesis. The energy of formation of the N–H · · · · O bond is ~2000 cal. and of the N–H · · · · N bond ~1930 cal. (Davies, *Ann. Reports*, 1946, **43**, 12), so that this factor alone does not entirely account for the differences in Arrhenius parameters. The formation of the transition states for the reactions of primary amines is probably attended by a greater increase of solvation than with pyridine. Again the essential structural feature appears to be amino-hydrogen. The observed differences therefore probably arise from an interplay of solvation and a " net *ortho* effect," the resultant of steric hindrance, where operative, and hydrogen-bond formation.

Influence of the Structure of the Halogeno-compound on the Parameters of the Arrhenius Equation.—When nucleophilic attack on an aromatic carbon atom occurs, it is probable that the facilitation of the bond-forming process is of major importance. Structural changes reducing electron density at the seat of substitution facilitate these reactions. Consider first the results for the reactions of pyridine assembled in Table 3 and below.





E (cal.)	16 700	16 900	18 100	18 700

Entropies of activation are nearly the same, except for the reaction of 4-chloro-3-nitropyridine, which reacts faster with pyridine than does chloro-2 : 4-dinitrobenzene, by virtue of a somewhat increased value of *A*. Replacement of a *p*-nitro-group by a " *p* "-cyclic nitrogen atom leaves the energy of activation virtually unchanged, but increases *A*, whereas a corresponding change in the *ortho*-position increases *E* by 1400 cal., despite the disappearance of steric hindrance, and leaves *A* unchanged. From the *para*-position the mainly tautomeric effect of a cyclic nitrogen atom is much the same as that of a nitro-group. Considering the *ortho*-position, we ascribe the energy difference (the above figure is the minimum value of the magnitude to be connected with polar effects) to the fact that the *o*-nitro-group operates through a powerful inductive effect and a weakened tautomeric effect, whereas the " *o* "-cyclic nitrogen atom operates through a weak electromeric effect

(*o*-quinonoid contribution to transition state). When, in 2-chloropyridine, a nitro-group is shifted from the position *para* to the chlorine to one *ortho* to it, only a slight increase in energy of activation ensues (reactions 8 and 13, Table 3), despite the intervention of steric hindrance, *i.e.*, the contribution of polar factors to E probably falls, whereas a similar shift of a cyclic nitrogen atom increases the energy of activation by 1800 cal., and lowers A (reactions 14 and 13, Table 2). This is a fundamental difference between nitro-groups and cyclic nitrogen atoms. It renders intelligible the properties, for example, of 2- and 4-chloropyrimidines: 4-chloropyrimidine is very unstable because it readily reacts with itself, whereas 2-chloropyrimidine, having no "*p*"-cyclic nitrogen, reacts with measurable speed with a base as strong as piperidine.

With primary amines as reagents, replacing an *o*-nitro-group by a cyclic nitrogen atom increases the energy of activation by 1800—2600 cal. depending on the amine, A being hardly affected. These reactions are virtually free from steric hindrance, and the differences arise from the structural differences in the halogeno-compounds discussed above and possibly differences in the energy of hydrogen-bond formation in the transition state. The reactions of 2-chloro-3-nitropyridine with primary amines are rather complicated and we defer further discussion of these results until our studies with chloro-2 : 6-dinitrobenzene are complete. It is, however, noteworthy that 2-chloro-3-nitropyridine reacts rather faster with primary amines than does 2-chloro-5-nitropyridine, but the reverse is true for reactions with pyridine.

Finally, we compare the reactions of the chloronitropyridines with those of the chloronitrobenzenes. Direct comparison is impossible because of lack of results with the chloronitrobenzenes. However, the reactions of *o*- and *p*-chloronitrobenzene with aqueous ammonia have energies of activation of 20 500 and 21 400 cal. respectively (Vorozhtov, Jr., and Kobelev, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 1465) and with piperidine in ethanol the corresponding values are about 18 000 cal. (Chapman, Parker, and Soanes, *Chem. and Ind.*, 1951, 148). The value for aniline will probably exceed 20 000 cal. We may estimate therefore that replacement of cyclic $\geqslant$CH by cyclic nitrogen *para* to chlorine in *o*-chloronitrobenzene will reduce the energy of activation for reaction with aniline by at least 9000 cal., on the assumption that the energies of activation for a hypothetical uncatalysed reaction of aniline with 4-chloro-3-nitropyridine would be approximately the same as for the reaction with chloro-2 : 4-dinitrobenzene, and for the corresponding change in the *ortho* position the reduction will be at least 7000 cal.

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UNIVERSITY COLLEGE, SOUTHAMPTON. [*Received, August 17th*, 1951.]

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86. *Experiments with Halogenated* o-*Benzoquinone Derivatives.*

By ALEXANDER SCHÖNBERG and NAZIH LATIF.

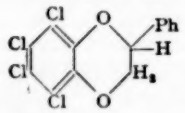
(i) Tetrabromo-*o*-benzoquinone reacts with acenaphthylene in hot benzene to give the compound (IV).

(ii) Tetrabromo- and tetrachloro-*o*-benzoquinone and 4-triphenylmethyl-1 : 2-benzoquinone are rapidly reduced by Grignard reagents to the corresponding catechols.

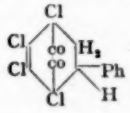
(iii) The reactions of 9-diazofluorene and of ethyl diazoacetate with various *o*-benzoquinone derivatives to give substituted benzodioxoles are described.

(i) HORNER and MERZ (*Annalen*, 1950, **570**, 89) found that styrene and tetrachloro-*o*-benzoquinone undergo a Diels–Alder condensation in the dark in boiling benzene to give (II) (yellow, m. p. 133°), whereas in sunlight (I) (colourless, m. p. 79°) is formed (Schönberg *et al.*, *J.*, 1951, 1364). Unlike (II), (I) does not form a quinoxaline derivative.

The reaction leading to (I) [cf. (*A*)] is characteristic of many photo-reactions (Schönberg and Mustafa, *J.*, 1944, 387; 1945, 551; 1947, 997) and in rare cases may also take place in the dark (Schönberg and Latif, *J. Amer. Chem. Soc.*, 1950, **72**, 4828).



(I)

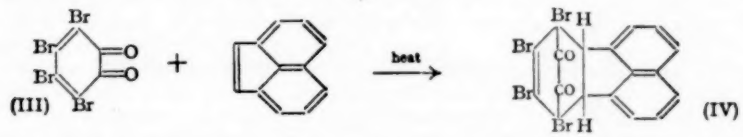


(II)

When tetrabromo-*o*-benzoquinone (III) is treated with acenaphthylene in boiling benzene, a deep yellow addition product, 7 : 8 : 9 : 10-tetrabromo-6*b* : 7 : 10 : 10*a*-tetrahydro-7 : 10-*endo*oxalylfluoranthene (" Ring Index " numbering) (IV), which forms a quinoxaline

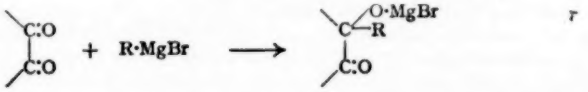
(*A*)

derivative, is obtained in good yield; (IV) seems to be an analogue of a substance obtained by Horner and Merz (*loc. cit.*) from tetrachloro-*o*-benzoquinone and acenaphthylene, but they did not assign a name or a structure to it. (IV) may be useful as a starting material for the syntheses of compounds related to fluoranthene.



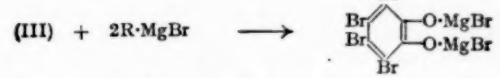
(III) (IV)

(ii) *Reduction of o-Benzoquinone Derivatives by Grignard Reagents.*—1 : 2-Diketones and *o*-quinones react with Grignard reagents, at least in the first stage of the reaction, according to (*B*). Such reactions have been observed with diacetyl, benzil, *cyclo*pentane-

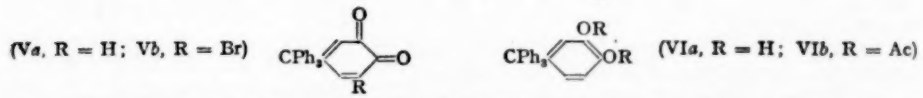


(*B*)

1 : 2-dione, camphorquinone, phenanthraquinone, and acenaphthenequinone (see Courtot in Grignard's " Traité de Chimie Organique," 1937, Vol. 5, pp. 386—390). We find that tetrabromo- and tetrachloro-*o*-benzoquinone and 4-triphenylmethyl-1 : 2-benzoquinone (V*a*) react with Grignard solution as shown in (*C*). When these intensely coloured quinones in ether or benzene are added in portions to an excess of Grignard solution, each portion reacts vigorously and decolorisation takes place immediately. When the product is decomposed, the corresponding catechol derivative is obtained (*e.g.*, VI*a* from V*a*). For further identification the catechol derivatives were converted into their diacetyl derivatives, *e.g.*, (VI*b*).



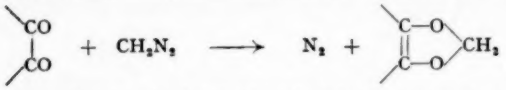
(*C*)



(V*a*, R = H; V*b*, R = Br) (VI*a*, R = H; VI*b*, R = Ac)

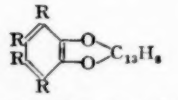
(ii) *Action of 9-Diazofluorene and of Ethyl Diazoacetate on o-Benzoquinone and 1 : 2-Naphthaquinone Derivatives.*—In a number of cases reactions between *o*-quinones and diazomethane and diphenyldiazomethane have been carried out [see (*D*)], but the reactions mentioned in the side-heading have not been reported. We find that phenanthraquinone is

remarkably stable to diazofluorene under the conditions in which it reacts with diphenyldiazomethane according to (*D*) (Schönberg and Mustafa, *J.*, 1946, 746). However, tetrachloro-

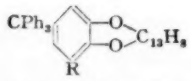


(*D*)

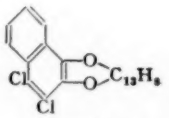
and tetrabromo-*o*-benzoquinone, 4-triphenylmethyl-1 : 2-benzoquinone (V*a*), 3-bromo-5-triphenylmethyl-1 : 2-benzoquinone (V*b*), and 3 : 4-dichloro-1 : 2-naphthaquinone react vigorously with 9-diazofluorene, giving, in good yield, the compounds (VII*a*), (VII*b*), (VIII*a*), (VIII*b*), and (IX) respectively. These products are colourless or nearly so; their constitution is based on analogy (cf. Schönberg, Awad, and Latif, *J.*, 1951, 1368) and on the fact that (VII*b*) can also be obtained by reaction between tetrabromocatechol and 9 : 9-dichlorofluorene.



(VII*a*, R = Cl; VII*b*, R = Br) *

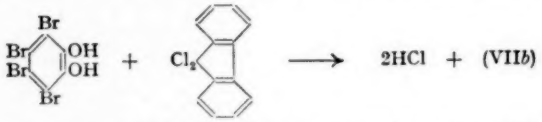


(VIII*a*, R = H; VIII*b*, R = Br) *

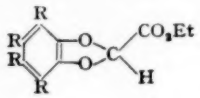


(IX) *

* In these structural formulæ, $C_{13}H_8$ represents a 9-fluorenylidene residue.



When tetrachloro- or tetrabromo-*o*-quinone is treated with ethyl diazoacetate, a reaction according to (*D*) takes place, leading to the colourless 2-carbethoxy-4 : 5 : 6 : 7-tetrahalogenobenzodioxole (X*a* or *b*).



(X*a*, R = Cl; X*b*, R = Br)

Experimental

(i) *Reaction between Tetrabromo-o-benzoquinone and Acenaphthylene.*—The quinone (0·9 g. and acenaphthylene (0·4 g.) in dry benzene (30 c.c.) were refluxed for one hour. After concentration, 7 : 8 : 9 : 10-*tetrabromo*-6b : 7 : 10 : 10a-*tetrahydro*-7 : 10-endo*oxalylfluoranthene* (IV) was obtained, and recrystallised from xylene in yellow crystals, m. p. 250°; it was dried at 100° before analysis (90% yield) (Found: C, 37·5; H, 1·7; Br, 55·7. $C_{18}H_8O_3Br_4$ requires C, 37·4; H, 1·4; Br, 55·6%). When (IV) in xylene was refluxed with water and left to cool, colourless crystals were obtained which became yellow when heated in a bath at 190° and gave the same m. p. and mixed m. p. as the yellow substance mentioned above: the colourless product is probably a hydrate.

The yellow or the colourless substance (1 mol.) was dissolved in a hot mixture of equal parts of methyl alcohol and glacial acetic acid, and a hot concentrated solution of *o*-phenylenediamine (3 mols.) in methyl alcohol added. After a few seconds, precipitation of a yellow crystalline *quinoxaline* derivative occurred; after being washed with boiling xylene, it had m. p. 260° (decomp.) (Found: C, 44·6; H, 1·7; N, 3·7; Br, 49·7. $C_{24}H_{12}N_2Br_4$ requires C, 44·4; H, 1·9; N, 4·3; Br, 49·4%).

When 5 : 6 : 7 : 8-tetrachloro-2-phenylbenzodioxen (I) was similarly treated with *o*-phenyllenediamine, no quinoxaline derivative was obtained.

(ii) *Action of Grignard Reagents on o-Benzoquinone Derivatives.*—(a) *Tetrabromo-o-benzoquinone and phenylmagnesium bromide.* To an ethereal solution of phenylmagnesium bromide (from bromobenzene, 3 mols.) was added in portions an ethereal solution of tetrabromo-*o*-benzoquinone (Zincke, *Ber.*, 1887, **20**, 1777) (1 mol.); a vigorous reaction took place and the colour of the quinone faded after each addition. The mixture was then refluxed for one hour,

decomposed with ice and dilute hydrochloric acid, and extracted with ether. The extract was washed with water and dried, and the ether evaporated. To the residue a few c.c. of benzene were added; crystals of tetrabromocatechol separated on cooling, and recrystallised from benzene in almost colourless crystals, m. p. 182—185° (yield about 75%) (Found: C, 17·4; H, 0·7. Calc. for $C_6H_2O_2Br_4$: C, 16·9; H, 0·5%). When boiled with acetic anhydride, this gave colourless crystals of the diacetyl derivative of tetrabromocatechol (m. p. and mixed m. p. 213°).

(b) *Tetrabromo-o-benzoquinone and ethylmagnesium iodide.* This reaction was carried out similarly to the preceding one and the bromocatechol (80% yield) was identified as before (Found: C, 17·2; H, 0·8%).

(c) *Tetrachloro-o-benzoquinone and phenylmagnesium bromide.* The experiment was carried out as for the tetrabromo-analogue. The dried ethereal solution was evaporated, the residue dissolved in hot benzene, and the solution left to concentrate slowly at room temperature; the semi-solid crystalline substance formed was washed with cold benzene, then with light petroleum (b. p. 40—60°), and recrystallised from benzene, forming colourless crystals of tetrachlorocatechol (Found: C, 28·7; H, 1·2. Calc. for $C_6H_2O_2Cl_4$: C, 29·0; H, 0·8%), identified by m. p. and mixed m. p., 190°, of its diacetyl derivative.

(d) *4-Triphenylmethyl-1 : 2-benzoquinone and ethylmagnesium iodide.* To an ethereal solution of ethylmagnesium iodide (from ethyl iodide, 3·5 mols.) was added the quinone (Zincke and Wugk, *Annalen*, 1908, **363**, 284) (0·7 g.) in dry benzene; an immediate reaction took place, and after 30 minutes the reaction mixture was decomposed with ice and dilute hydrochloric acid and extracted with benzene. The dried benzene extract was concentrated and left to cool; the crystals which separated, m. p. 250—255°, were boiled with acetic anhydride for one hour and then set aside; crystals of 4-triphenylmethylcatechol diacetate (VI*b*) (Zincke and Wugk, *loc. cit.*) separated (m. p. and mixed m. p. 195°).

(iii) *Reaction of o-Quinone Derivatives with 9-Diazofluorene and with Ethyl Diazoacetate.*—(a) *Reactions of 9-diazofluorene.* (1) With tetrabromo-*o*-benzoquinone. To a solution of the quinone (0·6 g.) in benzene (10 c.c.) was added diazofluorene (Schönberg, Awad, and Latif, *loc. cit.*) (0·6 g.); immediately a vigorous evolution of gas took place. After a few minutes **9 : 9-***(tetrabromo-o-phenylenedioxy)fluorene* (VII*b*) separated; it recrystallised from xylene in colourless crystals, m. p. above 310° (yield almost quantitative). It was difficultly soluble in cold benzene, alcohol, or acetone (Found: C, 39·1; H, 1·6; Br, 54·2. $C_{19}H_8O_2Br_4$ requires C, 38·7; H, 1·3; Br, 54·4%).

(2) With tetrachloro-*o*-benzoquinone. The quinone (0·4 g.) (Jackson and MacLaurin, *Amer. Chem. J.*, 1907, **37**, 7) was dissolved in benzene (8 c.c.), and diazofluorene (0·6 g.) added; a vigorous reaction took place and after a few minutes (VII*a*), the *chloro*-analogue of the above, separated and was recrystallised from benzene, forming colourless crystals, m. p. 281°, difficultly soluble in cold acetone or alcohol (yield almost quantitative) (Found: C, 55·9; H, 2·1; Cl, 34·6. $C_{19}H_8O_2Cl_4$ requires C, 55·6; H, 1·9; Cl, 34·6%).

(3) With 3-bromo-5-triphenylmethyl-1 : 2-benzoquinone. To the quinone (0·3 g.) (Zincke and Wugk, *loc. cit.*) suspended in benzene (5 c.c.) was added a slight excess of diazofluorene; the mixture was gently warmed on the water-bath for a few seconds and set aside for 3 days. The crystalline deposit was filtered off, washed with acetone, and recrystallised from benzene. **9 : 9-(3-***Bromo-5-triphenylmethyl-o-phenylenedioxy)fluorene* (VIII*b*) was obtained in colourless crystals, m. p. 262°, difficultly soluble in cold acetone or benzene (70% yield) (Found: C, 77·2; H, 4·5. $C_{38}H_{25}O_2Br$ requires C, 76·8; H, 4·3%).

(4) With 4-triphenylmethyl-1 : 2-benzoquinone. The quinone (0·2 g.) was treated with diazofluorene (0·2 g.) in benzene (10 c.c.) as previously described. After 3 days the benzene was driven off under reduced pressure, a few c.c. of cooled acetone were added, and the mixture was cooled in ice. **9 : 9-(4-***Triphenylmethyl-o-phenylenedioxy)fluorene* (VIII*a*) separated and recrystallised from ice-cooled acetone in colourless crystals, m. p. 250° (50% yield) (Found: C, 88·4; H, 5·0. $C_{38}H_{26}O_2$ requires C, 88·6; H, 5·1%).

(5) With 3 : 4-dichloro-1 : 2-naphthaquinone. Diazofluorene (0·8 g.) in benzene (15 c.c.) and the quinone derivative (0·5 g.) (Zincke and Engelhardt, *Annalen*, 1894, **283**, 347) were left at room temperature for 4 days, during which the solvent evaporated. The residue was washed with ice-cold acetone several times and recrystallised from acetone; **9 : 9-(3 : 4-***dichloro-1 : 2-naphthylenedioxy)fluorene* (IX) separated in almost colourless crystals, m. p. about 255° (70% yield) (Found: C, 70·5; H, 3·1; Cl, 18·1. $C_{23}H_{12}O_2Cl_2$ requires C, 70·5; H, 3·1; Cl, 18·1%).

(6) With phenanthraquinone. To the quinone (0·5 g.) in benzene or chloroform (10 c.c.) diazofluorene (0·8 g.) was added, but after a week's standing the quinone was recovered unchanged.

(b) *Reactions of diazoacetic ester.* (1) With tetrachloro-*o*-benzoquinone. Diazoacetic ester (2·5 c.c.) in ether was added to a solution of the quinone (1 g.) in benzene (10 c.c.) and left overnight. The ether was driven off, and the benzene solution refluxed for 30 minutes; a few drops of methyl alcohol were added and the mixture was left overnight. The solution was evaporated under reduced pressure, and the residue dissolved in methyl alcohol and left to cool. *Ethyl 4 : 5 : 6 : 7-tetrachlorobenzodioxole-2-carboxylate* (X*a*) separated, and recrystallised from light petroleum (b. p. 40—60°) in colourless crystals, m. p. 82° (Found: C, 36·5; H, 2·0; Cl, 42·0. $C_{10}H_6O_4Cl_4$ requires C, 36·0; H, 1·8; Cl, 42·6%).

(2) With tetrabromo-*o*-benzoquinone. By similar means the *tetrabromo*-analogue (X*b*) was obtained; it was washed with methyl alcohol and recrystallised from light petroleum (b. p. 40—60°), forming almost colourless crystals, m. p. 121—122° (Found: C, 24·0; H, 1·3; Br, 63·3. $C_{10}H_6O_4Br_4$ requires C, 23·5; H, 1·2; Br, 62·7%).

Reaction of 9 : 9-*Dichlorofluorene with Tetrabromocatechol.*—Dichlorofluorene (1·25 mol.) and tetrabromocatechol (1 mol.) were heated (protected from moisture) in a boiling-water bath for 15 minutes. The product was dissolved in boiling xylene, and the solution filtered, concentrated, and left to cool; 9 : 9-(*tetrabromo-o-phenylenedioxy*)*fluorene* (VII*b*) separated in crystals, m. p. above 310° (yield 80%) (Found: C, 38·2; H, 1·4. $C_{19}H_8O_2Br_4$ requires C, 38·7; H, 1·3%).

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87. *Gold Imides.*

By AMIN M. TYABJI and (the late) CHARLES S. GIBSON.

Auric imides of the type $M^I[AuX(imido)_3]$ (X = halogen) from succinimide, and of the type $M^I[AuX_2(imido)_2]$ from *o*-benzoicsulphonimide (saccharin) and phthalimide have been prepared, and their reactions, especially towards hydrolytic agents, studied.

THE present communication reports observations on complex salts formed by reaction between alkali gold halides and cyclic imides containing a five-atom ring, and the products of their hydrolysis. The complexes obtained are similar in type to the succinimido-gold complexes described by Pope (B.P. 338 506/1929; U.S.P. 1 809 384/1931), but no compound of the type $M^I[Au(imido)_4]$ as claimed by Kharasch and Ishbell (*J. Amer. Chem. Soc.*, 1931, **53**, 3059), where imido = $C_6H_4(CO)(SO_2)N-$ or $C_6H_4(CO)_2N-$, was isolated. From both Pope's observations and our own, it would appear that the central gold atom is unable to accommodate four such bulky groups within its orbit.

Baeyer and Co. (D.R.-P. 347 139, 348 070) describe a saccharino- and a sulphonamido-saccharino-compound of gold. A formula has only been given for the latter product, and it should be modified to, *e.g.*, $\{[NH_2{\cdot}SO_2{\cdot}C_6H_3(CO)(SO_2)N]_3 \equiv Au \leftarrow OH_2\}$, if it can be shown to be unimolecular, in order to conform to the well-established structural formula for quadricovalent auric compounds of the type $B \rightarrow AuX_3$ where B = R_3N, R_2S, R_2O, R_3P, RCN, or similar electron donor (cf. Obituary Notice, Gibson, *J.*, 1951, 625; Mann and Purdie, *J.*, 1940, 1235; Henke, *Annalen*, 1858, **106**, 280).

On mixing of an aqueous solution of an alkali auric halide with succinimide, saccharin, or phthalimide, together with an equivalent of alkali, or alternatively, with the alkali salt of the imide, crystalline complexes were obtained, and the composition of these remained constant whatever proportions of the reactants were chosen. However, only the most convenient preparatory methods have been recorded below.

Potassium bromoaurate and potassium succinimide afforded the new compound, potassium trisuccinimidobromoaurate (I), which is similar to Pope's compound (II; R = alkyl or H), but differs from it in being a salt. It was quite stable in aqueous solution, and was unaffected by recrystallisation from boiling water, from which it was obtained in colourless crystals, though the solutions were yellow. With saccharin and phthalimide in

place of succinimide, the new compounds, potassium bis-*o*-benzoicsulphonimidodibromoaurate (III) and potassium diphthalimidodibromoaurate (IV), were obtained. It will be seen that these compounds correspond to Pope's $\{[(CH_2{\cdot}CO)_2N]_2AuX_2\}M^I$ (X = halogen).

$\{[(CH_2{\cdot}CO)_2N]_3AuBr\}K$ (I)

$\{[(CH_2{\cdot}CO)_2N]_3Au \leftarrow NH_2R\}$ (II)

$\{[C_6H_4(CO)(SO_2)N]_2AuBr_2\}K$ (III)

$\{[C_6H_4(CO)_2N]_2AuBr_2\}K$ (IV)

Although (III) is sufficiently stable to allow of its isolation from hot aqueous solutions in the form of red crystals, yet it cannot be recrystallised, for it is decomposed by hot water (by a sort of " disproportionation ") to the original bromoaurate and the insoluble white compound, monoaquotris-*o*-benzoicsulphonimidogold (V) :

$$3\{[C_6H_4(CO)(SO_2)N]_2AuBr_2\}K + 2H_2O = 2\{[C_6H_4(CO)(SO_2)N]_3Au \leftarrow OH_2\} + 2KBr + KAuBr_4 \quad (V)$$

The hydrolysis is incomplete, as the supernatant liquid becomes acid in reaction, and the gold content of (V) is low. Calcium bis-*o*-benzoicsulphonimidodichloroaurate formed a yellow microcrystalline powder, which decomposed in a similar manner when heated with water. The decomposition product was not investigated. The corresponding sodium salt, on the other hand, resisted hydrolysis by boiling water. The solutions exhibited the interesting property of forming stable yellow gels on cooling. These gels were re-formed when the yellow powder was dissolved in hot water and the solution then allowed to cool.

The compound (IV) was so susceptible to hydrolysis that some decomposition was unavoidable during its preparation, but its solubility in acetone enabled easy separation from the product of hydrolysis, which could be obtained in quantity by using an excess of alkali in the preparation of (IV). The free acid gave correct analyses for diphthalimidodihydroxyauric acid (VI), soluble in hot water and in aqueous alcohol, differing in this

$\{[C_6H_4(CO)_2N]_2Au(OH)_2\}H$ (VI)

respect from (V), which appeared to be non-ionic. In view of the easy hydrolysis of phthalimide to phthalamic acid (Landsberg, *Annalen*, 1882, **215**, 197; Boon and Leigh, *J.*, 1951, 1500), this compound is possibly a derivative of phthalamic acid.

Thus a certain gradation becomes apparent both in the capacity of the cyclic imides to co-ordinate with gold halides on the one hand and in the relative stability of the bromogold imides on the other. The succinimide complex is the most stable, containing three imido-groups besides the halogen, whereas the other two imides studied afford complexes of the type $[(imido)_2AuX_2]M^I$. The derivative from saccharin undergoes a curious type of hydrolysis to the aquo-complex $\{[C_6H_4(CO)(SO_2)N]_3Au \leftarrow OH_2\}$, whereas the phthalimido-anologue suffers simple replacement of the two halogen by hydroxyl groups.

Experimental

Potassium Trisuccinimidobromoaurate (I).—(*a*) Potassium bromoaurate (5 g.) in water (10 ml.) was mixed with a solution of succinimide (2·4 g., 3 mols.) in an equivalent quantity of N-potassium hydroxide. When the clear solution was cooled to 0°, yellowish crystals separated, which were washed at the pump and recrystallised from boiling water to afford a colourless crystalline powder of the *potassium* salt (I) (Found: C, 22·7; H, 2·3; N, 6·5; Br, 13·1; Au, 31·3. $C_{12}H_{12}O_6N_3BrKAu$ requires C, 23·6; H, 2·0; N, 6·9; Br, 13·1; Au, 32·3%).

(*b*) Potassium bromoaurate (2·5 g.) in water (10 ml.) was mixed with potassium succinimide (2·5 g., 3 mols.), and the mixture warmed and then cooled; the resulting crystals were recrystallised as above (Found: Br, 13·5; Au, 31·9%). The salt suffers no apparent change when heated to 250°. The aqueous solutions are yellow and, after warming, acid in reaction.

o-*Benzoicsulphonimide* (*Saccharin*) *Derivatives.*—*Potassium bis-o-benzoicsulphonimidodibromoaurate* (III). This preparation has to be carried out in dilute solution, as the product cannot be recrystallised. Potassium bromoaurate (2·9 g.) in water (30 ml.) was mixed with the potassium derivative of saccharin (2·2 g.) in water (30 ml.). When the hot solution was cooled to 0°, a red microcrystalline precipitate was formed. This was filtered off, washed with cold water, and dried (yield 44%). When heated, the product darkened and sintered above 220°. Four separate

preparations were analysed (Found: Br, 21·0, 21·7, 22·0, 21·6; Au, 25·6, 25·8, 25·5, 25·4. $C_{14}H_8O_6N_2Br_2S_2KAu$ requires Br, 21·0; Au, 25·9%).

Though sufficiently stable to be isolated from hot aqueous solutions of the components, the *potassium* salt underwent profound changes when its aqueous solutions were boiled for a time: the solutions became acid and dark from the presence of bromoaurate ions. The new colourless crystalline compound formed, too insoluble to be recrystallised, was impure *monoaquotris-o-benzoicsulphonimidogold* (Found: N, 5·6; S, 11·5; Au, 23·8. $C_{21}H_{14}O_{10}N_3S_3Au$ requires N, 5·5; S, 12·6; Au, 25·9%).

Sodium bis-o-benzoicsulphonimidodichloroaurate was similarly prepared by mixing warm aqueous solutions of sodium chloroaurate (1 mol.) and the sodium derivative of saccharin (2 mols.). The salt occasionally separated as a canary-yellow powder, but usually as a gel. When heated, the *sodium* salt sintered at about 230° and was partly molten at 245° (Found: Cl, 10·5; Au, 29·1. $C_{14}H_8O_6N_2Cl_2S_2NaAu$ requires Cl, 10·8; Au, 30·1%). The corresponding *calcium* salt was similarly prepared from calcium chloroaurate (2 g.) in hot water (30 ml.) and the potassium salt of saccharin (2·2 g.) in hot water (30 ml.). The yellow microcrystalline compound sintered when heated to 225° and then decomposed slowly (Found: Cl, 10·9; Au, 29·1. $C_{28}H_{16}O_{12}N_4Cl_4S_4CaAu_2$ requires Cl, 10·9; Au, 30·2%). This substance was also decomposed by boiling in water, the insoluble product not being investigated.

Phthalimide Derivatives.—Potassium diphthalimidodibromoaurate (IV). When boiling solutions of potassium bromoaurate (1 mol.) and potassium phthalimide (2 mols.) or phthalimide and an equivalent of potassium hydroxide (2 mols.) were mixed and cooled, a yellow precipitate was formed, which was separated by means of acetone into two components: an insoluble, white, minor portion (see below) and a soluble major portion consisting of the yellow *potassium diphthalimidodibromoaurate* (Found: Br, 24·1; Au, 28·7. $C_{16}H_8O_4N_2Br_2KAu$ requires Br, 23·2; Au, 28·8%). The corresponding *acid* was prepared as follows: To a boiling solution of potassium bromoaurate (5 g.) was added potassium phthalimide (3·5 g., 2 mols.), the mixture cooled, the yellow precipitate filtered off, dried, dissolved in acetone, filtered from a small quantity of insoluble matter, and the salt precipitated by addition of ligroin. After one repetition of the acetone treatment, the substance was dissolved in boiling water, in which it is sparingly soluble, the solution filtered, and the clear filtrate treated with the calculated amount of hydrochloric acid and set aside to crystallise. The sample for analysis was further purified by one treatment with acetone (Found: N, 4·5; Br, 23·3, 23·2; Au, 30·5. $C_{16}H_9O_4N_2Br_2Au$ requires N, 4·3; Br, 24·6; Au, 30·3%). Both the acid and the potassium salt behave similarly on heating: they darken above 200° and yield a white sublimate of phthalimide.

Diphthalimidodihydroxyauric acid (VI). The white, insoluble compound (above) is the only product when double the amount of alkali is used in the preparation of (IV), the solution becoming decolorised when the reaction is complete. The compound was also prepared from (IV) by heating it with the calculated amount of potassium hydroxide solution in acetone and diluting it with water. The free *acid* was obtained on recrystallising the salt from hot water or aqueous alcohol containing sulphuric acid. Three different preparations were analysed (Found: C, 36·5, 36·6, 36·1; H, 2·7, 2·9, 2·6; N, 5·4, 5·0, 5·5; Au, 37·3, 37·7, 36·9. $C_{16}H_{11}O_6N_2Au$ requires C, 36·6; H, 2·1; N, 5·3; Au, 37·6%). The behaviour on heating is similar to that of the dibromo-compound.

Attempts to repeat Kharasch's Experiments.—Gold hydroxide (1·5 g., prepared according to Figurier; see Gmelin–Kraut's "Handbuch," V, 2, p. 262) and the sodium derivatives of saccharin (8 g.) were heated together with water for 5 days. No reaction had taken place, for the colourless residue obtained on evaporating the filtered solution did not contain any gold whatsoever. A similar result was obtained by heating together gold hydroxide (1·25 g.), phthalimide (3 g., 4 mols.) and 1 equiv. of sodium carbonate in water (100 ml.) for 24 hours on a water-bath.

The cost of this investigation, carried out in 1936, has been met by grants from Imperial Chemical Industries Limited. Thanks are offered to Dr. F. H. Brain for valuable suggestions and criticism during the preparation of this paper.

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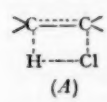
88. *Stereospecificity in Thermal Elimination Reactions. Part II.* The Pyrolysis of (−)-Menthyl Chloride.*

By D. H. R. Barton, A. J. Head, and R. J. Williams.

The pyrolysis of (−)-menthyl chloride to furnish a mixture of (+)-*p*-menth-2- and -3-enes and hydrogen chloride has been studied by both static and dynamic methods. In reactors coated with a carbonaceous film the reaction has been proved to be homogeneous and unimolecular in mechanism. The rate-constant equation can be represented by the expression $k = 10^{12\cdot6}e^{-45{,}000/RT}$ sec.$^{-1}$. The ratio of Δ^2- to Δ^3-olefin formed is approximately 1 : 3. The production of the latter hydrocarbon confirms the correlation previously propounded between stereospecificity of thermal elimination and reaction mechanism. In clean-walled reactors the much faster heterogeneous decomposition of (−)-menthyl chloride has been shown to follow a different reaction path.

In Part I * of this series it was concluded that thermal elimination reactions which were unimolecular † in mechanism should show, where the molecular structure was otherwise appropriate, a *cis*-stereospecificity of elimination. From the stereochemical point of view there was already at that time an adequate number of examples of *cis*-elimination in the pyrolysis of methyl xanthates and of benzoates (cf. Barton and Rosenfelder, *J.*, 1949, 2459; 1951, 1048) to substantiate our conclusion. However, up to the present, in no case has the *mechanism* of elimination been established for a thermal reaction of known stereospecificity. The examples already cited could, in principle, be heterogeneous reactions, in which case *no* theoretical conclusion as to the stereospecificity of elimination would have been justified.

Now, in a series of papers (Barton, Head, Howlett, Onyon, and Williams, *J.*, 1949, 148, 155, 165; *Trans. Faraday Soc.*, 1949, **45**, 725, 735; 1950, **46**, 114; *J. Amer. Chem. Soc.*, 1950, **72**, 988; *J.*, 1951, 2033, 2039) on the pyrolysis of saturated chlorinated hydrocarbons it has been shown that hydrogen chloride is smoothly eliminated with the formation of olefin or chlorinated olefin. There are three general mechanisms for these reactions: (i) heterogeneous decomposition (on glass), (ii) homogeneous unimolecular decomposition, (iii) homogeneous radical-chain decomposition. Normally, mechanism (i) is much faster than (ii) or (iii), but by using reactors coated with a carbonaceous film, it can be reduced to insignificance. The course of homogeneous reaction then followed depends only on the molecular structure of the substrate. If either the latter, or the products of reaction, are inhibitors for mechanism (iii), then the chlorinated hydrocarbon decomposes by the alternative unimolecular mechanism (ii). From these generalisations it can, for example, be concluded that (−)-menthyl chloride should be pyrolysed by the unimolecular mechanism, since the menthenes produced would be inhibitors for the radical-chain type of decomposition. In the unimolecular mechanism the four-centre transition state must be as represented in (*A*). As we have emphasised previously (Barton, *loc. cit.*), quantum-mechanical theory suggests that, for a minimisation of activation energy, the four centres should lie in one plane. In suitable *cyclo*hexane derivatives this implies that *cis*- should take preference over *trans*-elimination.



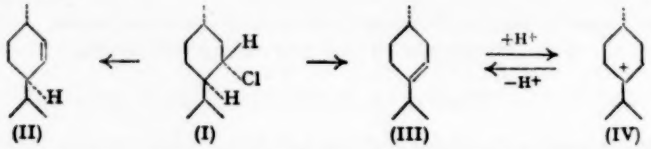
(*A*)

In this connection we were particularly interested in the pyrolysis of (−)-menthyl chloride (I) because the elegant work of Hückel, Tappe, and Legutke (*Annalen*, 1940, **543**, 191) has shown that the mixtures of (+)-*p*-menth-2- and -3-enes, (II) and (III), respectively, which would be formed in this reaction, are readily analysed by taking

* The paper by Barton (*J.*, 1949, 2174) is regarded as Part I of this series.

† The term unimolecular is again used in the sense employed by physical chemists in dealing with gas-phase reactions, not in the sense commonly used for discussing heterolytic reactions.

advantage of the facile acid-catalysed racemisation of the Δ^3-isomer through the symmetrical carbonium ion (IV).



It is true that the formation of *two* olefins from the pyrolysis implies that two different transition states must be involved. However, both reactions would be expected to have the same, unimolecular, mechanism and to exhibit first-order kinetics. The difference in the rate-constant equation for the two reactions would be too small to be detected experimentally as a curved Arrhenius plot (cf. Barton and Onyon, *J. Amer. Chem. Soc.*, 1950, **72**, 988). It should be mentioned that, since *cis*-elimination towards, usually takes preference over *cis*-elimination away from, a bridge-head (cf. Barton, *loc. cit.*) the (+)-*p*-menth-3-ene should be the preponderant reaction product.

The aim of the present work, then, was (*a*) to confirm that the mechanism of pyrolysis of (−)-menthyl chloride (in coated reactors) was unimolecular, and (*b*) to show that this led to the formation of a mixture of (+)-*p*-menth-2- and -3-enes in which the latter predominated. Although both hydrocarbons would be formed through a transition state of type (*A*), only the formation of the Δ^3-isomer would constitute an unambiguous demonstration of *cis*-elimination of hydrogen chloride. If *trans*-elimination were the preferred mode of reaction, as in (say) alkoxide-induced elimination (Hückel *et al.*, *loc. cit.*), then (+)-*p*-menth-2-ene alone would be formed.

Experimental

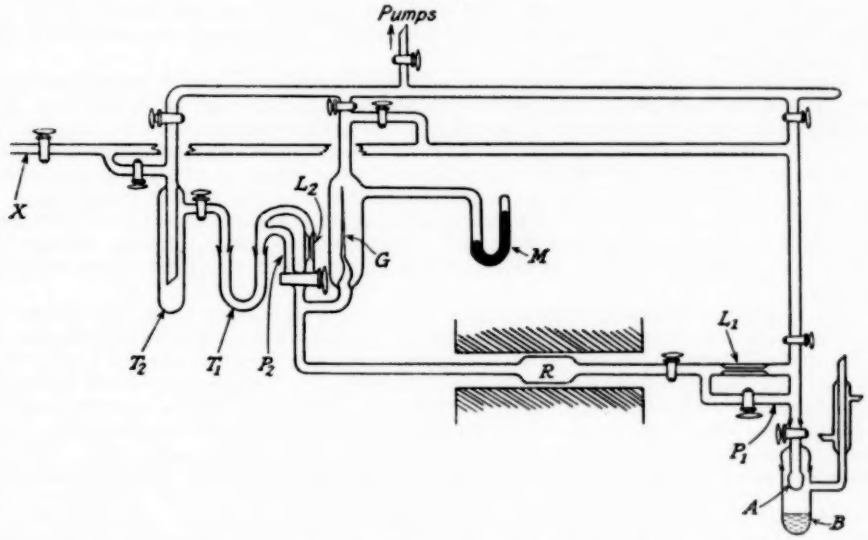
Materials.—(−)-Menthyl chloride was prepared according to the directions of Hückel and Pietrzok (*Annalen*, 1939, **540**, 250). It had b. p. 88·5°/12·5 mm., n_D^{22} 1·4634, d_4^{26} 0·9349, $[\alpha]_D$ −50·2° (homogeneous). This material was used for the static experiments. For the dynamic work a slightly less pure fraction, $[\alpha]_D$ −48·4° (homogeneous), was employed in the majority of the experiments.

Apparatus.—(i) *Static experiments.* The apparatus and general technique have already been described in detail by Barton and Howlett (*J.*, 1949, 155). Because of the lower vapour pressure of (−)-menthyl chloride it was found advantageous to modify the ordinary storage trap by incorporating a 250-ml. bulb, the whole being immersed in a heated oil-bath. This provided a larger reservoir of heated vapour and, with the oil-bath at 110°, it was easily possible to introduce 20 mm. of the (−)-menthyl chloride vapour. All connecting tubes from the trap to the reactor and the necessary taps were, of course, electrically heated as before. Some modification of the method of measuring pressure was also introduced. The spoon gauge, still used as a null-point instrument, was made more sensitive, and the differential pressures were measured by using a small closed-limb manometer in conjunction with a cathetometer. In all experiments mercury was employed as thermostatic vapour. The kinetics of the reaction were elucidated by following the increase in pressure at constant volume as in our previous work on chlorinated hydrocarbon pyrolysis.

(ii) *Dynamic experiments.* The apparatus employed is illustrated in Fig. 1. It was constructed throughout in Pyrex glass. The (−)-menthyl chloride was stored in a detachable trap, *A*, which was heated by the reflux apparatus, *B*. In all experiments steam was used as thermostatic vapour; the temperature of the (−)-menthyl chloride remained constant to 0·1° in any run. The (−)-menthyl chloride vapour was passed through the previously calibrated capillary leak L_1 (to which a by-pass P_1 was also attached) and then into the reaction vessel *R*, which was heated as indicated in an electric furnace. The reactor itself was constructed of two long 2-mm. bore lengths of tubing attached to a short length of 30-mm. bore tubing which constituted the main reactor volume. The length and position of the latter were so adjusted that the main reactor volume was at constant temperature (within 1°) and placed at the position of maximum temperature in the furnace. On either side of the main reactor volume the temperature fell off quite rapidly. The main reactor volume comprised 21·6 ml. In order to allow for any reaction occurring in the narrow-bore connecting tubing the lengths of connecting

tubing (and hence the volumes) were observed at which, by calculation, it was known that the reaction would proceed at an average of $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$, etc., of the velocity in the main reactor volume. By weighting these volumes accordingly, it was computed that the effective volume of the whole reactor was 22·7 ml. Although this method of computation is only approximate, the errors involved in the estimate of the extra 1·1 ml. are so small relative to the main reactor volume (21·6 ml), that the effect of the approximations is negligible. The temperature of the furnace was manually controlled and measured by a base-metal thermocouple. The gases issuing from the furnace were passed through a second, previously calibrated capillary leak L_2, then through a trap T_1 cooled in solid carbon dioxide–alcohol mixture, which served to condense the menthenes and any unchanged (−)-menthyl chloride, and finally through a liquid-nitrogen-cooled trap T_2 in which the hydrogen chloride was condensed. Oxygen-free nitrogen was admitted through X when required. During a run the apparatus was pumped continuously by a two-stage mercury pump backed by an oil pump, the pumps being attached as indicated. In order to facilitate evacuation of the reactor itself, a by-pass P_2 was used. The pressure in the reactor during a run was measured by a spoon gauge G which was employed as a null-point

FIG. 1.



instrument. The actual pressure readings were obtained with the aid of the closed-limb mercury manometer M which was read (to 0·1 mm.) with a cathetometer. Other connections and taps were as indicated in Fig. 1 All taps and joints in contact with vapours were lubricated with silicone high-vacuum grease. All tubing and taps, the spoon gauge, and other parts of the apparatus in contact with (−)-menthyl chloride vapour or its decomposition products, but not heated by the furnace, were heated by suitable nichrome-wire windings to such a temperature (at least 100°) as to prevent any condensation.

The technique for conducting experiments was as follows. (−)-Menthyl chloride was introduced into the storage trap and thoroughly outgassed by repeated freezing and evacuation. The (−)-menthyl chloride trap was then weighed and replaced on the apparatus. The apparatus was evacuated with both by-passes open, and the null-point of the spoon gauge determined. The by-pass P_2 was closed, and the run commenced by opening the tap of the (−)-menthyl chloride trap, and then closing the by-pass P_1. At the end of the run the tap of the (−)-menthyl chloride trap was closed and all gases in the reactor tubing were rapidly pumped (<5 secs.) into the collecting traps T_1 and T_2, the by-passes being used. The traps A and T_1 were detached, cleaned, and weighed. The hydrogen chloride collected in trap T_2 was swept out by a stream of nitrogen into water and titrated with N/20-potassium hydroxide. At the temperature of trap T_1 the vapour pressure of liquid hydrogen chloride is about 2 atm. This made it unlikely that any hydrogen chloride would be condensed in T_1, but this was confirmed in two ways.

First, at the end of a run the traps T_1 and T_2 were left open to each other in the evacuated state to ensure complete equilibration. Secondly, the hydrogen chloride in a typical run [92% decomposition of the (−)-menthyl chloride] collecting in trap T_1 was determined and found to be negligible [less than 0·09 mg. for the decomposition of 303 mg. of (−)-menthyl chloride]. The success of the technique depends, however, on seeing that all parts of the apparatus are thoroughly dry. The average flow rate of (−)-menthyl chloride was about 150 mg. per hour, and runs were made for 2—3 hours in each case.

The analysis of the mixture of menthenes and (−)-menthyl chloride in trap T_1 was carried out as follows. The liquid contents were rinsed quantitatively with chloroform into a 10-ml. volumetric flask and made up to the mark. The rotation of this solution was then measured in a 1-dm. tube. From this determination, and with a knowledge of the percentage decomposition of (−)-menthyl chloride (see above) and hence the amount of (−)-menthyl chloride condensed in trap T_1, it was possible to compute the amounts of (+)-*p*-menth-2- and -3-enes formed, it being assumed, of course, that no racemisation had occurred. Since, however, the rotation of (+)-*p*-menth-2-ene ($[\alpha]_D$ +132°) is rather close to that of (+)-*p*-menth-3-ene ($[\alpha]_D$ +109°) (see Hückel *et al.*, *loc. cit.*) this procedure was not very accurate. A more reliable measure of the (+)-*p*-menth-3-ene content was obtained by racemisation. This was effected by Hückel *et al.* (*loc. cit.*) by refluxing with toluene-*p*-sulphonic acid in ethanol solution. We found that the following procedure was more convenient. Its accuracy was checked by using the toluene-*p*-sulphonic acid method.

Approximately 5 ml. of the above-mentioned chloroform solution were placed in a graduated tube, one drop of water added, and hydrogen chloride gas passed through for 30 minutes. Most of the hydrogen chloride (and some of the chloroform) was then removed *in vacuo*; the turbidity of the solution was destroyed by adding a small piece of anhydrous calcium chloride and leaving the whole to stand. The dried chloroform solution was transferred to a further graduated tube with adequate rinsing and made up to the original mark, and the rotation determined again. In numerous preliminary experiments it was established (*a*) that the chloroform had to be saturated with water to ensure racemisation (thorough drying led to no, or only partial, racemisation) and (*b*) that repetition of the treatment specified above caused no further change in optical rotation.

The rotation after racemisation was due to (−)-menthyl chloride (of known amount and $[\alpha]_D$), of racemised (+)-*p*-menth-3-ene, and of (+)-*p*-menth-2-ene (of unknown amount, but of known $[\alpha]_D$). It was possible therefore to calculate the amounts of the two hydrocarbons present. Furthermore, from the rotation of the solution before racemisation, and the information obtained from the racemisation, the rotation of the (+)-*p*-menth-3-ene originally produced in the pyrolysis could be calculated. This procedure assumed that the rotations of the (+)-*p*-menth-2- and -3-enes were the same in chloroform and in the homogeneous state. This was checked by measurements on mixtures of menthenes (see later) and on (−)-menthyl chloride.

Results

Static Experiments.—(i) *Stoicheiometry.* By analogy with previous work in our series of papers on the pyrolysis of chlorinated hydrocarbons (see, especially, Barton, *J.*, 1949, **148**; Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725; Barton and Head, *ibid.*, 1950, **46**, 114) it was expected, with some certainty, that (−)-menthyl chloride would decompose according to the equation

$$C_{10}H_{19}Cl \longrightarrow C_{10}H_{18} + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

to furnish a mixture of (+)-*p*-menth-2- and -3-enes and hydrogen chloride. This was confirmed in the static experiments when it was shown (Table 1) that the final pressure (p_f) in the reactor after a long run was close to twice the initial pressure (p_0). A more extensive justification of this stoicheiometry is given below.

Table 1.*

Temp., °K.	614	614	614	624	624	624
p_0, mm.	16·7	16·7	18·7	12·5	14·2	14·9
p_f/p_0	2·09	2·05	2·05	2·03	2·17	2·09
Temp., °K.	624	624 †	624	624	624	—
p_0, mm.	15·6	16·5	19·4	26·3	26·7	—
p_f/p_0	2·10	2·21	2·04	2·11	2·06	—

* Reaction time 15 hours in each case unless stated to the contrary, except where denoted by †, where it was 45 hours.

(ii) *Kinetics.* The kinetics of the decomposition were studied in both empty and packed reactors, the latter having an approximately five-fold increase in surface area/volume ratio. As with our previous experience in the pyrolysis of chlorinated hydrocarbons (see, especially, Barton and Onyon, *loc. cit.*), the decomposition of (−)-menthyl chloride was fast and of indefinite kinetic order in clean-walled glass reactors. This heterogeneous mode of decomposition was slowly repressed by repeated experiments and, after about 60 runs, reproducibility was finally attained. The reaction then showed first-order kinetics as illustrated in Fig. 2, with no indication

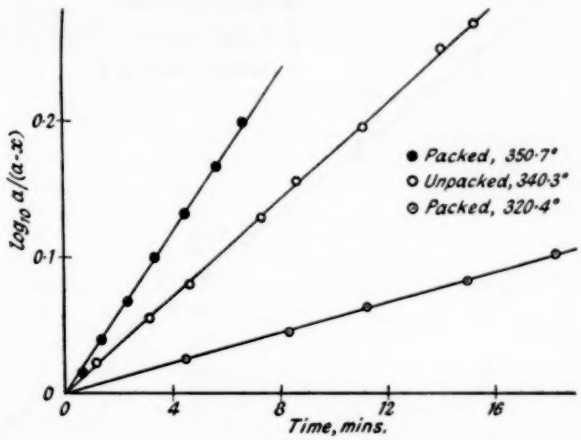
TABLE 2.*

p_0, mm.	5·9	14·4	23·3	31·5
$k \times 10^3$, sec.$^{-1}$	0·44	0·40	0·40	0·40

* All experiments at 608·2° K in the packed reactor.

of induction periods. It was generally found more satisfactory to avoid thorough evacuation of the reactor, the products of a run being left in until just before the next run. The reactor was then evacuated for 4—5 minutes to a pressure of 10^{-2} mm. This procedure is comparable

FIG. 2.



with that employed by Brearly, Kistiakowsky, and Stauffer (*J. Amer. Chem. Soc.*, 1936, **58**, 43) in studying the pyrolysis of *tert.*-butyl chloride. Within the limited pressure range accessible, the first-order rate constant was independent of initial pressure (see Table 2). The rate-constant data over the temperature range 592·9° to 623·9° K are summarised in Table 3

TABLE 3.

Temp., ° K	No. of runs	Mean $k \times 10^3$, sec.$^{-1}$	% Standard deviation of mean k *
Unpacked reactor.			
603·3	5	0·383	0·7
613·9	13	0·720	1·4
Packed reactor.			
592·9	22	0·209	1·4
608·8	13	0·464	1·4
623·9	21	1·26	4·0

* Given by $100 \times \sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}} \Big/ \bar{x}$ where the symbols have the usual significance.

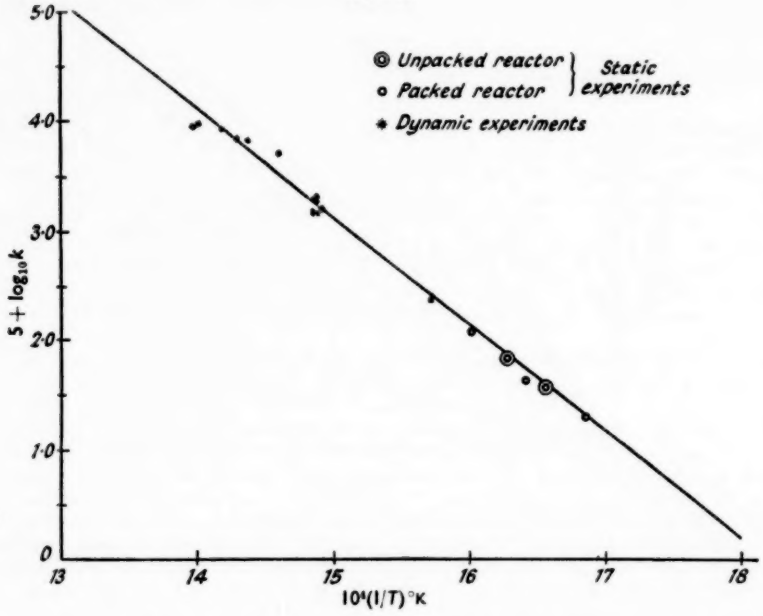
TABLE 4.

p_0, mm., of (−)-menthyl chloride	p_0, mm., of C_3H_6	C_3H_6, %	$k \times 10^3$, sec.$^{-1}$	p_0, mm., of (−)-menthyl chloride	p_0, mm., of C_3H_6	C_3H_6, %	$k \times 10^3$, sec.$^{-1}$
Unpacked reactor at 613·9° K.				Packed reactor at 609·2° K.			
—	0	0	0·720	—	0	0	0·420
14·2	5·4	38	0·720	16·7	11·4	68	0·425
11·4	6·4	56	0·725	15·5	13·8	89	0·420

and illustrated graphically in Fig. 3. The best straight line through the points, drawn by visual inspection, indicated an approximate rate constant equation of $10^{12\cdot6}e^{-42,600/RT}$ sec.$^{-1}$. The homogeneity of the reaction is clearly demonstrated and, having regard to the experimental difficulties of the study, the reproducibility of the results must be regarded as satisfactory. The addition of propylene, even in major amounts, had no effect on the rate of decomposition (see Table 4) in either the packed or the unpacked reactors.

Dynamic Experiments.—(i) *Stoicheiometry.* As further evidence for the stoicheiometry of equation (1), the dynamic experiments were conducted in such a way as to furnish a materials balance. The results, summarised with other data in Table 5, show that in no case was more than 2·5% of material lost. For the purposes of calculation the loss was assumed to be in the menthene fraction which, in most experiments, was the major product of the reaction. As mentioned above, the results permit the calculation of the rotation of (+)-*p*-menth-3-ene. The fact that this is in fair agreement (see p. 461) with the best literature values supports the

FIG. 3.



stoicheiometry assumed in the calculation. Finally an ultra-violet spectroscopic examination (with the Unicam S.P. 500 Spectrophotometer) revealed no indication of conjugated menthadienes or of *p*-cymene in the reaction products. The same result was obtained with the products from the heterogeneous decomposition (see further, p. 459).

(ii) *Kinetics.* The first runs in a clean-walled reactor, not unexpectedly, showed rates much above those calculated from the rate-constant equation of the static experiments. This effect was eliminated by leaving approximately 15 mm. of (−)-menthyl chloride in the reactor overnight at 500°, a slight carbonaceous film then being slowly deposited on the reactor walls. After approximately 20 runs, the rates of decomposition became reproducible and the rate constants were in fair agreement with those calculated by extrapolation from the static experiments. The rate constants were calculated, first-order kinetics being assumed, by the equation already given (*J.*, 1949, 148). The results for 16 consecutive runs, omitting two only, are summarised in Table 5 and further in Fig. 3. The overall rate-constant equation for both static and dynamic runs (see Fig. 3) can be represented by the expression $k = 10^{12\cdot6}e^{-45,000/RT}$, in good agreement with the equation deduced solely on the basis of the static experiments.

(iii) *Experiments on the heterogeneous decomposition of* (−)-*menthyl chloride.* These experiments were carried out in a packed reactor of effective residual volume 20·2 ml. The surface area/volume ratio was six times that in the unpacked reactor. The whole apparatus and

TABLE 5. *Homogeneous mechanism of decomposition.*

Run no.	Temp., °K.	*p*, mm.	Contact time, sec.	De-comp., %	$k \times 10^5$, sec.$^{-1}$	% lost	(+)-*p*-Menth-2-ene, %	$[\alpha]_D$ of (+)-*p*-menth-3-ene, calc.
22	672	9·7	22·0	37·6	2·14	2·1	—	—
23	671	10·7	24·5	33·8	1·68	1·3	—	—
24	672	11·0	25·7	39·8	1·97	0·7	—	—
25	673	10·3	22·6	33·5	1·53	0·0	—	—
26	672	13·1	20·8	33·9	1·53	1·9	—	—
27	673	10·6	22·3	38·5	1·62	0·2	—	—
28	673	11·0	23·9	38·5	2·04	0·9	—	—
30	705	12·3	22·4	86·1	8·8	0·0	26	+ 88°
31	714	11·8	21·3	87·2	9·6	1·7	29	+106
32	700	11·7	21·9	78·8	7·1	0·0	28	+ 96
33	716	12·3	24·2	89·0	9·2	1·1	29	+105
35	636	9·6	22·8	5·4	0·24	1·4	—	—
36	696	12·7	24·1	81·3	7·0	2·5	30	+124
37	685	12·6	23·6	72·8	5·5	0·9	25	+109

packing were of clean Pyrex glass. The aim of the experiments was to study the nature of the products formed in the heterogeneous decomposition. The results are summarised in Table 6. As a means of summarising the results the data have been calculated as if the reaction followed first-order kinetics. Although this is probably only approximately the case (cf. Barton

TABLE 6. *Heterogeneous mechanism of decomposition.*

Run no.	Temp., °K.	*p*, mm.	Contact time, sec.	De-comp., %	$k \times 10^5$, sec.$^{-1}$	% lost	(+)-*p*-Menth-2-ene, %	$[\alpha]_D$ of (+)-*p*-menth-3-ene, calc.	$k/k_{calc.}$
Runs in clean glass reactor with no coating.									
1	645	11·6	21·3	88·8	10·3	—	7	+19	24
2	647	11·6	20·7	92·2	12·3	2·2	8	+ 5	26
3	645	12·6	21·2	92·3	12·1	1·5	—	—	28
After being coated overnight with 15 mm. of (−)-menthyl chloride at 743° K.									
4	661	12·5	20·3	76·5	7·1	1·9	17	+27	7
Coated overnight as before.									
5	691	13·1	19·8	88·9	11·5	2·2	19	+37	2·7
6	679	12·2	23·4	87·6	8·9	0·0	20	+18	3·7
Coated for 3 days at 773—803° K.									
7	692	12·0	20·5	81·8	8·3	0·0	20	+40	1·8
Coating destroyed with oxygen at 773° K.									
8	663	12·5	21·0	93·2	12·8	1·3	—	—	12

TABLE 7.

Treatment of menthene mixture	Temp., °K.	*p*, mm.	Contact time, sec.	$[\alpha]_D$ of product in $CHCl_3$
Experiments under homogeneous conditions.				
Before treatment	—	—	—	+43·1° (*c*, 0·64) *
Passed through furnace alone	694	9·9	18·1	+44·5° (*c*, 2·70)
Passed through furnace alone, but 101 mol. % of hydrogen chloride "bled in" after second capillary leak	695	9·5	18·9	+44·0° (*c*, 2·60)
Passed through furnace together with 100 mol. % of hydrogen chloride "bled in" after first capillary leak	694	11·5	23·8	+45·4° (*c*, 2·30)
Experiments under heterogeneous conditions.				
Passed through furnace with reactor surface giving heterogeneous decompn. 28 times as fast as homogeneous reaction	655	10·6	17·5	+44·1° (*c*, 3·80)
Passed through furnace with reactor surface giving heterogeneous decompn. 12 times as fast as homogeneous reaction together with 560 mol. % of hydrogen chloride "bled in" after first capillary leak	663	15	69	+43·3 (*c*, 1·60)

* $[\alpha]_D$ +43·2° ± 0·2° (homogeneous).

and Onyon, *loc cit.*), it serves to show that the heterogeneous rate of decomposition is much greater than the homogeneous rate. The final column in Table 6 gives the ratio of k for a particular run to $k_{calc.}$, the calculated rate constant (from Fig. 3) for the homogeneous mode of decomposition.

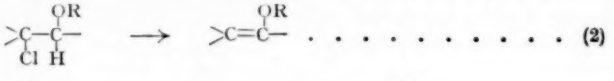
(iv) *Racemisation experiments.* As discussed in greater detail on p. 461, it was of importance to establish whether (+)-*p*-menth-3-ene would be racemised under the experimental conditions used. For this purpose a mixture of menthenes obtained as a by-product (Hückel *et al.*, *loc. cit.*) in the preparation of (−)-menthyl chloride was employed. By racemisation analysis (see above) this mixture contained 5% of (+)-*p*-menth-2-ene, 33% of (+)-*p*-menth-3-ene, and 62% of racemised *p*-menth-3-ene. The mixture was passed (*a*) through the empty reactor used for the homogeneous experiments of Table 5, and (*b*) through the packed reactor used for the heterogeneous experiments of Table 6. The results are summarised in Table 7. In no case was there any significant racemisation of the (+)-*p*-menth-3-ene.

Discussion

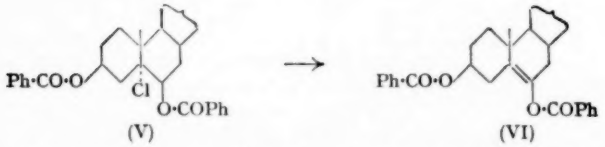
The thermal decomposition of (−)-menthyl chloride in reactors coated with a carbonaceous film follows first-order kinetics, the rate constants *not* varying with the initial pressure. The reaction is homogeneous, exhibits no induction periods even at the lowest temperatures studied, and is totally unaffected by the addition of propylene. All these experimental features are identical with those established previously for ethyl chloride, 1 : 1-dichloroethane, *n*- and *iso*-propyl chlorides, *n*- and *tert.*-butyl chlorides, and 1 : 2-dichloropropane (Barton and Howlett, *J.*, 1949, 165; Barton and Onyon, *Trans. Faraday Soc.*, 1949, **45**, 725; Barton and Head, *ibid.*, 1950, **46**, 114; Barton, Head, and Williams, *J.*, 1951, 2039), and, without repeating the arguments in detail, we regard them as adequate to prove that (−)-menthyl chloride decomposes by the unimolecular mechanism. As additional support for this conclusion it should be mentioned that the rate constant equation of $10^{12\cdot6}e^{-45{,}000/RT}$ sec.$^{-1}$, established for both static and dynamic experiments, is in good agreement with the linear $\log_{10} A$ versus E relationship reported to hold for the unimolecular mode of decomposition of chlorinated hydrocarbons by Barton, Head, and Williams (*loc. cit.*).

As demonstrated on p. 459, the homogeneous unimolecular thermal decompositions of (−)-menthyl chloride furnishes a mixture of (+)-*p*-menth-2- and -3-enes in the ratio of approximately 1 : 3. The formation of the latter compound is a clear demonstration of the correctness of our general thesis of the relationship between *cis*-elimination and unimolecularity of mechanism in thermal elimination reactions. The proportion of the Δ^2- to Δ^3-isomer is approximately the same as that given by the decomposition of the methyl xanthate (Hückel *et al.*, *loc. cit.*) although the mechanism of the latter reaction has not been rigidly established.

It seems probable that the related *cis*-elimination of hydrogen chloride in the pyrolysis of suitable *trans*-chlorohydrin derivatives according to (2) will prove a general phenomenon :



. . . . . (2)



(V) (VI)

As a specific example we mention the smooth pyrolysis of 5α-chlorocholestane-3β : 6β-diol dibenzoate (V) to furnish cholest-5-ene-3β : 6-diol dibenzoate (VI) (Lettré and Muller, *Ber.*, 1937, **70**, 1947; Petrow, Rosenheim, and Starling, *J.*, 1938, 677).*

* In a recent communication (Davis and Petrow, *J.*, 1949, 2536) it was stated that this reaction is best interpreted as *trans*-elimination of hydrogen chloride from 5β-chlorocoprostane-3β : 6β-diol dibenzoate, although there is, in fact, already ample evidence in the literature as to the correct stereochemistry of (V). In a personal communication Dr. V. Petrow has kindly indicated that he now withdraws his interpretation of *trans*-elimination in this pyrolysis.

From the experimental data summarised in Tables 5 and 6 it is possible to calculate the rotation of the (+)-*p*-menth-3-ene produced in each dynamic run. The rotations calculated for the homogeneous pyrolysis (Table 5) show a considerable scatter, though the mean value of +105° for $[\alpha]_D$ is in good agreement with the best literature value of +109° (see Hückel *et al.*, *loc. cit.*). To a certain extent this scatter is explained by the fact that all the errors, both of assumption for calculation purposes and of experimental technique, are concentrated in these figures. Further explanations would be provided if the reaction produced a small proportion of racemised *p*-menth-3-ene or if the latter hydrocarbon were racemised in the apparatus before analysis. The second alternative was excluded by the experiments summarised in Table 7. The first alternative, however, is a reasonable one as shown by the following evidence.

The much faster heterogeneous decomposition of (−)-menthyl chloride on clean, or only partly coated, glass walls (Table 6) afforded a menthene fraction which, if the usual analytical technique be applicable, contained somewhat less (+)-*p*-menth-2-ene than in the homogeneous decomposition, and a large proportion of racemised *p*-menth-3-ene. As the walls of the reactor were progressively coated and the rate of decomposition approached that of the homogeneous reaction, the content of non-racemised *p*-menth-3-ene increased. Again, various experiments with the latter hydrocarbon (see Table 7) demonstrated that the racemisation was *not* brought about after its genesis. The racemisation must therefore be an integral part of the heterogeneous reaction mechanism. The somewhat erratic values for the calculated $[\alpha]_D$ of (+)-*p*-menth-3-ene in the homogeneous decomposition (Table 5) may, therefore, be due in part to the intrusion of a minor percentage of heterogeneous decomposition.

We would emphasise, however, that we advance the thesis that the heterogeneous mode of decomposition on glass affords racemised *p*-menth-3-ene with reserve, because it is conceivable that other olefins are formed in this process. Thus the stereochemistry and conformation (cf. Barton, *Experientia*, 1950, **6**, 316) of (−)-menthyl chloride are suited to rearrangement to a five-membered-ring olefin. Be this as it may, these aspects of the heterogeneous decomposition reinforce our conclusion that, in the coated-wall reactors, we have indeed been studying a homogeneous reaction.

We thank the Government Grants Committee of the Royal Society and the Central Research Fund of London University for financial assistance. This work was carried out during the tenure of D.S.I.R. maintenance grants by two of us (A. J. H. and R. J. W.).

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, September 10th*, 1951.]

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89. *The Anodic Oxidation of Platinum at Very Low Current Density.*

By S. E. S. EL WAKKAD and (MISS) SAYEDA H. EMARA.

The results of various workers on the variation of the anode potential with the quantity of electricity passed when the platinum electrode is forced from hydrogen to oxygen evolution, as well as on the type of oxides formed on the surface of the metal before oxygen evolution, have been clarified by carrying out the anodic oxidation of platinum in acid, neutral, and alkaline solutions at very low current density by the direct potentiometric method, using a special cell and constant current unit.

A LIMITED amount of work has previously been carried out on the anodic oxidation of platinum. Bowden (*Proc. Roy. Soc.*, 1929, *A*, **125**, 446) showed that the change of the anode potential with the quantity of electricity passed occurring when the platinum electrode is forced from hydrogen to oxygen evolution was linear save for a slight break which was attributed to the formation of PtO_2 on the electrode. Butler and his co-workers (Butler and Armstrong, *ibid.*, 1932, *A*, **137**, 604; Armstrong, Himsworth, and Butler, *ibid.*, 1933, *A*, **143**, 89; Butler and Armstrong, *J.*, 1943, 743; Butler and Drever, *Trans. Faraday Soc.*,

1936, **32**, 427; Pearson and Butler, *ibid.*, 1938, **34**, 1163), on the other hand, distinguished stages for the ionisation of free and adsorbed hydrogen, the charging of a double layer, and finally the deposition of an adsorbed layer of oxygen. The results of Erschler, Frumkin, and their co-workers (Slygin and Frumkin, *Acta Physicochem. U.S.S.R.*, 1935, **3**, 791; 1936, **4**, 911; 1936, **5**, 819; Erschler and Proskurnin, *ibid.*, 1937, **6**, 195; Erschler, *ibid.*, 1937, **7**, 327; Erschler, Deborin, and Frumkin, *ibid.*, 1938, **8**, 565; *Trans. Faraday Soc.*, 1939, **35**, 464) are in general conformity with those of Butler *et al.* Recently Hickling (*Trans. Faraday Soc.*, 1945, **41**, 333), using his oscillographic method, showed that only PtO is formed on the surface of the anode before oxygen evolution begins. On the other hand, Altmann and Busch (*ibid.*, 1949, **45**, 720), using an undulant current, found by chemical analysis that the product was practically pure PtO_2,nH_2O.

In the present paper this point is clarified by studying the anodic oxidation of platinum in acid, neutral, and alkaline solutions at very low current density by the direct potentiometric method, using a special cell and constant current unit. By using an electrode of large surface area and a small current, a considerable time is required for the electrode to pass from the hydrogen- to the oxygen-evolution values and thus equilibrium potentials can be measured at each stage of the polarisation. From such a study it is shown that PtO is first formed over the surface of platinum, followed by PtO_2, before oxygen evolution occurs. The latter oxide is unstable, decomposing to PtO. The results have also been confirmed oscillographically.

Experimental

The Direct Potentiometric Method.—The circuit used in obtaining the variation of the potential of the anode with the quantity of electricity passed employed a pentode valve as a constant-current device, so the current passing was largely independent of changes in the back-e.m.f. of the electrode system. The current was supplied from a 240 v dry battery.

The electrolytic cell used was of Pyrex glass without rubber connections. It consisted of a vessel of *ca.* 500-ml. capacity provided with 5 openings. Three of these, which had mercury-sealed covers, were for the cathode compartment, the anode compartment, and the compartment for the syphon of the reference electrode respectively. These compartments were plugged with fine sintered-glass plugs to prevent contamination of the anolyte. The other openings were for gas-inlet and -exit tubes, the latter being fitted with a Bunsen valve.

The platinum anode was prepared by platinising a platinum foil of 1·8 sq. cm. with spongy platinum black. This was carried out in 1% platinum chloride solution at a high current density (30 milliamps./sq. cm. for 3 minutes). The spongy platinum deposited did not form a very thick layer and thus could be easily cleaned. The electrode was washed several times in conductivity water and then with the solution in which it would be studied before it was introduced in its compartment in the electrolytic cell. Each experiment was carried out with a freshly prepared electrode. The cathode was a platinum spiral which was placed in its compartment far enough from the anode to ensure uniform distribution of the polarising current at the anode surface.

Measurements have been carried out mainly with three electrolytes: 0·1N-sulphuric acid, 0·2M-KH_2PO_4 + 0·2M-Na_2HPO_4 buffer mixture of approx. pH 6·8, and 0·1N-sodium hydroxide, all prepared from " AnalaR " materials and conductivity water. The solution in the cell was boiled before use and cooled in an atmosphere of pure nitrogen to remove any dissolved oxygen.

The current used was 30 microamps. per electrode. In each solution three studies were carried out on each electrode—the anodic polarisation, the cathodic polarisation, and the anodic decay. In the case of the anodic polarisation, the electrode was first polarised cathodically until hydrogen was evolved and a constant potential recorded, so as to ensure the reduction of any oxide already present on the surface of the electrode during its preparation. The current was then reversed to start the anodic polarisation, and the potential of the anode was recorded as a function of time. The cathodic curves were obtained after the electrode had been anodically polarised until oxygen was evolved; the current was then reversed and the potential of the working electrode measured at suitable time intervals. In case of the anodic decay experiments, the electrode was polarised anodically until oxygen was evolved; the current was then interrupted and the potential was measured after various times. All the experiments were carried out in an atmosphere of pure nitrogen.

The reference half cell was a saturated calomel electrode prepared according to the directions

of Harned and Owen ("The Physical Chemistry of Electrolytic Solutions," 1943, p. 321). The electrolytic cell as well as the reference half cell were kept in an air-thermostat at 25° ± 0·01°. The e.m.f. was measured with a calibrated metre bridge and an Onwood mirror galvanometer having a sensitivity of 190 mm. per microamp.

The Cathode Ray Oscillographic Method.—Work with this method was carried out by one of us (El Wakkad) during a visit to Dr. A. Hickling (University of Liverpool) to whom the authors are greatly indebted. The circuit used was on the same principle as that previously used by Hickling and others (Hickling, *Trans. Faraday Soc.*, 1945, **41**, 333; 1946, **42**, 518; Hickling and Spice, *ibid.*, 1947, **43**, 762; Hickling and Taylor, *Faraday Soc. Discuss.*, 1947, **1**, 277; *Trans. Faraday Soc.*, 1948, **44**, 262; El Wakkad and Hickling, *ibid.*, 1950, **46**, 820); it records the variation of potential with the quantity of electricity passed prior to oxygen evolution. The anode used was a platinum wire sealed into a glass tube and mounted vertically; it had an apparent area of 0·1 sq. cm. and was approx. 1 cm. in length. Before use, it was cleaned with hot concentrated hydrochloric acid, hot concentrated nitric acid, and water, and finally heated to redness. The cathode was a platinum spiral of approx. 0·5 sq. cm. in area. Observations were made in an atmosphere of pure nitrogen in the solutions used in the direct potentiometric

FIG. 1.

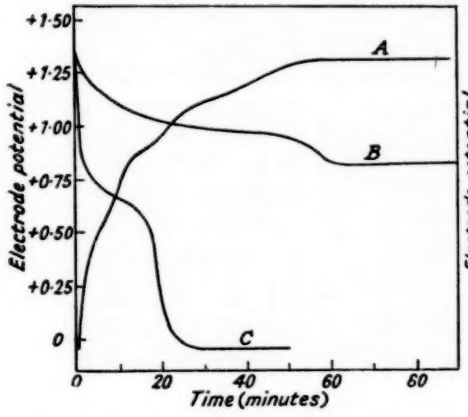
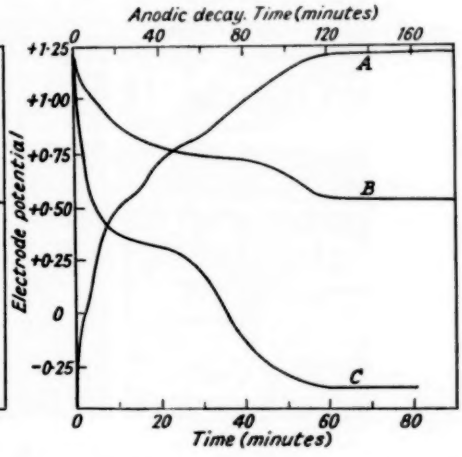


FIG. 2.



method. All experiments were carried out in a hut the temperature of which was constant at 25° ± 0·1°.

The results are shown as photographed oscillograms in which the ordinates represent potentials and the abscissæ are proportional to quantities of electricity passed. Suitable horizontal reference lines at intervals of 0·25 v were photographed immediately after the polarisation tracks, so that significant potentials can be read directly from the oscillograms. All potentials quoted are on the hydrogen scale. The quantity of electricity passed at any stage in the polarisation is obtained from the known capacity of the condenser in the circuit and the horizontal displacement which is governed by the voltage to which the condenser is charged. Suitable vertical lines at intervals of 10 v are shown, when necessary, to enable the quantity of electricity passed during the polarisation process to be calculated. In all cases a 5-μF condenser was convenient for the exhibition of a suitable polarisation track.

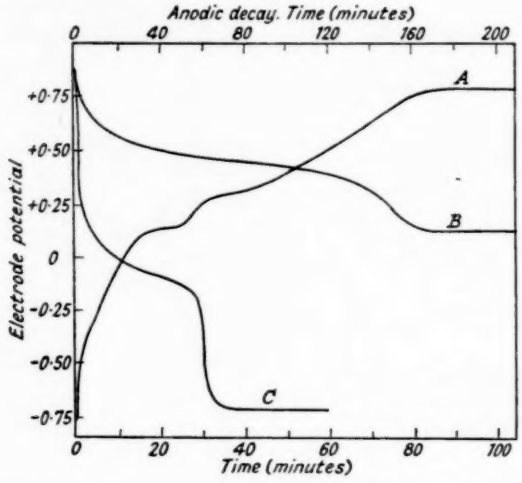
RESULTS AND DISCUSSION

Curve *A*, Fig. 1, is the characteristic anodic polarisation curve of platinised platinum at 25° with a polarising current of 30 μA, in 0·1N-sulphuric acid. Curve *A* of Fig. 2 is the same anodic polarisation curve in phosphate buffer of pH 6·8, and curve *A* in Fig. 3 is the anodic polarisation curve in 0·1N-sodium hydroxide. From these curves, which show the variation in the potential of the platinum anode with quantity of electricity passed, it can be seen that at first there is a rapid initial build-up of potential [ascribable to the charging of the double layer (Hickling, *loc. cit.*)] which is followed by two well-defined arrests before

oxygen evolution. Measurements from a large number of polarisation curves in 0·1N-sulphuric acid gave an average value of double layer capacity of ~18 000 μF per apparent sq. cm. of our platinised platinum electrode. In phosphate buffer solution the average value was of the same order as in 0·1N-sulphuric acid while in 0·1N-sodium hydroxide the average value was ~30 000 μF. The first arrest appears to start at a potential of 0·82 v in 0·1N-sulphuric acid, at 0·50 v in the phosphate buffer, and at 0·12 v in 0·1N-sodium hydroxide. The second arrest appears to start at potentials of 1·05, 0·70, and 0·30 v in the three solutions respectively.

Figs. 4, 5, and 6 give the characteristic oscillograms for the anodic polarisation of platinum at 25° in 0·1N-sulphuric acid, phosphate buffer of pH 6·8, and in 0·1N-sodium hydroxide with a polarising current density of 100 μA/sq. cm. The spots on the extreme left of each photograph show the steady hydrogen and oxygen evolution potentials at the same current density. From these oscillograms it can be seen that before oxygen evolution there are the following three stages: (1) a rather short period of constant potential, followed by a slow and somewhat irregular but reproducible rise of potential; (2) a rapid build-up

FIG. 3.



of potential; and (3) a somewhat slow rise of potential accompanied by two steps, which are well-defined in 0·1N-sulphuric acid, but comparatively ill-defined in neutral or alkaline solution.

The first stage can be attributed as in previous studies (Pearson and Butler, *loc. cit.*) to the ionisation of free and adsorbed hydrogen; it was not observed by the direct potentiometric method. This may be due to the fact that a platinum electrode subjected to alternate anodic and cathodic polarisation (as in the oscillographic study) is normally in an active state (Bowden, *Proc. Roy. Soc.*, 1929, *A*, **125**, 456), whereas in the direct potentiometric method each experiment was carried out with a freshly prepared electrode. Also there is the possibility that the time intervals in the potentiometric study were too large to record these steps.

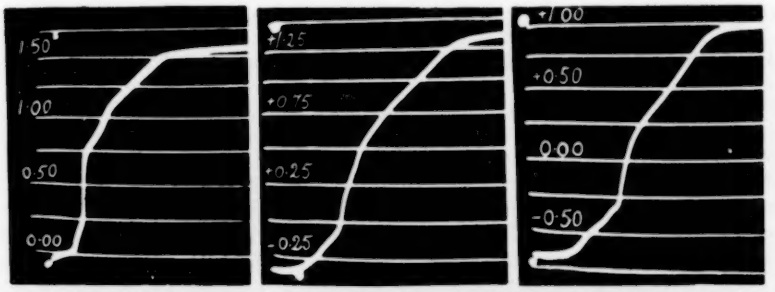
The second stage has been ascribed to the charging of the double layer. Measurements of a large number of oscillograms in 0·1N-acid gave an average value for the capacity of ~200 μF per apparent sq. cm. of smooth platinum, which agrees with the values quoted by Pearson and Butler and by Hickling (*locc. cit.*). In phosphate buffer and in 0·1N-alkali the change in potential appears to be less rapid and the capacity in such solutions is between 400 and 500 μF per apparent sq. cm.

The fact that there are two steps in the third stage is of great importance. The first step appears to start at a potential of 0·80 v in 0·1N-acid, at 0·50 v in phosphate buffers,

and at 0·15 v in 0·1N-alkali. The second arrest appears to start at potentials of 1·07, 0·75, and 0·35 v in the three solutions respectively.

In the annexed table the starting potentials of the first arrest obtained by the direct potentiometric and by the oscillographic method are compared with the equilibrium potential of the system Pt–PtO in the same solutions. The latter were obtained from Grube's results (*Z. Elektrochem.*, 1910, **16**, 621) after application of the ordinary equation for variation of potential with pH. The agreement between the starting potentials of the first arrest obtained by both methods with the equilibrium potentials of the system

FIG. 4. FIG. 5. FIG. 6.



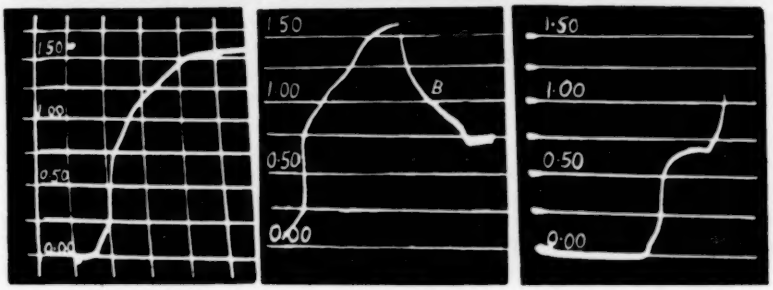


FIG. 7. FIG. 8. FIG. 9.

Pt–PtO indicates that this step in the anodic polarisation corresponds to the formation of PtO.

Solution	pH	Starting potential of first step, potentiometric, v	Starting potential of first step, oscillographic, v	Equilibrium Pt–PtO potential
0·1N-H_2SO_4	1	0·82	0·80	0·82
Phosphate buffer	6·8	0·50	0·50	0·49
0·1N-NaOH	13	0·12	0·15	0·13

In the direct potentiometric method, the quantity of electricity passed from the beginning of the first step to the beginning of the second step was in all solutions about 15 000 μC per apparent sq. cm. This is sufficient for the liberation of about $4·7 \times 10^{16}$ atoms of oxygen; if the diameter of the platinum atom is taken as $2·5 \times 10^{-8}$ cm. (from the specific gravity) there should be about $1·6 \times 10^{15}$ atoms of metal per sq. cm. at a platinum surface. A rather crude estimate of the ratio of the real to the apparent area of our platinised platinum electrode can be obtained from the value of the capacity of the double layer at the electrode in 0·1N-sulphuric acid, compared with that of smooth platinum in the same solution. The ratio of the real to the apparent area at a smooth platinum surface has been previously estimated by different observers as between 1·5 and 3, and the value of 2 is usually taken as an average. If the difference between the capacity of our platinised platinum electrode used in the direct potentiometric method and the smooth platinum electrode used in the oscillographic experiments is

assumed to be due to the difference in the true surface areas, the ratio of the real to the apparent area of our platinised platinum electrode will be about 180. This shows that the quantity of electricity passed in the first step corresponds to the formation of less than a unimolecular layer of PtO on the surface of the platinum. The oscillographic results also lead to this conclusion. In this case the quantity of electricity passed at any stage is computed from the known capacity of the condenser used and the horizontal displacement, which is governed by the voltage to which the condenser is charged. Fig. 7 shows the standard anodic track of smooth platinum in 0·1N-sulphuric acid, together with the vertical reference lines at intervals of 10 v. The quantity of electricity passed during the formation of PtO was found as a result of measurements of several oscillograms to be equal to about 250 μC per apparent sq. cm. This is sufficient for the liberation of about 8×10^{14} atoms of oxygen. The ratio of real to apparent area being assumed as 2, the quantity of electricity passed again corresponds to the formation of less than a unimolecular layer of PtO on the surface of the platinum electrode.

In the light of the previous studies of the anodic polarisation of metals (Hickling *et al.*, *loc. cit.*; El Wakkad and Hickling, *loc. cit.*) one would expect the step following the formation of PtO to be due to the formation on the surface of the metal of an oxide higher than PtO, and the potential recorded to correspond to an equilibrium potential between the higher oxide and PtO. From the starting potentials of the two steps as given above, the second step in each solution is seen to be about 0·2 v more positive that than of the Pt–PtO potential in the same solution. The potential of the system, $Pt(OH)_2 = PtO_2 + 2H^+ + 2e^-$, has been estimated to be *ca.* 1·1 v (Latimer, " The Oxidation States of the Elements and their Potentials in Aqueous Solutions," New York, 1938, p. 196), compared with 0·88 v for the system Pt–PtO. Thus, provided that the ordinary equation for the variation of the oxide potential with pH applies, the equilibrium potential between PtO and PtO_2 will always be about 0·2 v more positive than that of the system Pt–PtO. This suggests that the second step is due to the formation of PtO_2. Further evidence as to the nature of the second step can be obtained from the study of the anodic decay. Curves *B* in Figs. 1, 2, and 3, and section *B* in the oscillogram, Fig. 8, represent such anodic decays. These curves reveal that on interruption of the polarising current when the anode was at oxygen evolution potential, the potential did not drop directly to that of the system Pt–PtO but that it halted first at the PtO–PtO_2 potential, confirming the existence of a higher oxide over the surface of the electrode. However, after a certain time (which varies from one solution to another) the potential dropped further to the Pt–PtO value, indicating that the PtO_2 formed at the surface of the electrode during its anodic polarisation is rather unstable. The quantity of electricity passed in the second step (for the formation of PtO_2) obtained potentiometrically or oscillographically is always of the same order as that passed in the first step. This suggests that in the second step the PtO previously formed is further oxidised to PtO_2.

The existence of the PtO_2, has not, however, been recognised in any of the cathodic polarisation curves obtained either by the direct potentiometric method (curves *C* in Figs. 1, 2, and 3) or oscillographically (Fig. 9). On reversal of the current to make the oxide-covered electrode cathodic, the potential dropped directly and showed only one arrest at about the potential of the system Pt–PtO. This behaviour is not, however, unexpected owing to the unstable nature of the PtO_2 as revealed from the anodic decay curves.

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90. *Experiments on the Synthesis of Simple* C-*Substituted Derivatives of Dihydroxyacetone.*

By J. R. Marshall and James Walker.

Recorded observations concerning the anomalous course of reactions designed to yield derivatives of 1 : 3-dihydroxy-1-phenylacetone from *O*-acetylmandelyldiazomethane have been largely confirmed and extended. The diacetate and 3-monoacetate have now, however, been obtained. 1-Phenylpropane-1 : 2-dione and, probably, *O*-acetylmandelaldehyde were obtained together with the diacetate; the 3-monoacetate readily underwent decomposition to give 1-phenylpropane-1 : 2-dione. A mechanism is suggested for the formation of the diketone which can be applied to the analogous conversion of dihydroxyacetone into methylglyoxal.

When the protecting *O*-acetyl group was removed from 1-diazoacetyl-*cyclo*hexyl acetate by alkaline hydrolysis, the resulting diazo-ketone decomposed on treatment with acetic acid to give, as major product, 1-oxa-*spiro*[3 : 5]nonan-3-one; the mechanism of this reaction is discussed and analogies are provided. Evidence for the formation of the parent oxetan-3-one from chloroacetyldiazomethane was obtained.

With a view to use in the synthesis of analogues of cortisone, a study has been made of the application of the diazo-ketone synthesis to the chlorides of *O*-acylated derivatives of two representative α-hydroxy-carboxylic acids, mandelic acid and *cyclo*hexanol-1-carboxylic acid. This reaction, however, is unlikely to be of value in the synthesis of cortisone itself in view of the inaccessibility of appropriate 17-hydroxyetianic acids in the correct stereochemical configuration, as well as the difficulty of protecting a non-acylable 17α-hydroxyl group (cf. Fieser, *Experientia*, 1950, **6**, 312) and the unfavourable stereochemical course of the cyanohydrin reaction when applied to 17-keto-steroids.

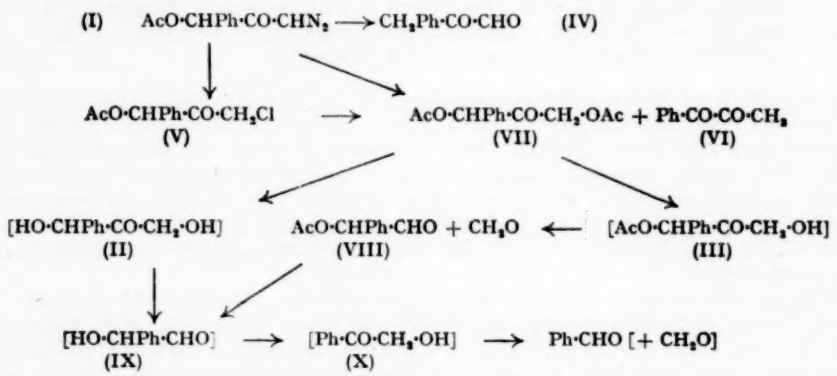
Although the diazo-ketone synthesis has been used successfully in the synthesis of L-sorbose from diethylidene L-lyxonoyl chloride (Gätzi and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 186), of D-erythrulose from *iso*propylidene D-glyceroyl chloride (Iwadare, *Bull. Chem. Soc. Japan*, 1939, **14**, 131), and of a series of homologous ketoses from the appropriate fully acetylated aldonyl chlorides (Wolfrom *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 201, 632; 1942, **64**, 1701, 2329; 1943, **65**, 1021, 1516; 1944, **66**, 204; 1945, **67**, 1793; 1946, **68**, 791, 1453), Bradley and Eaton (*J.*, 1937, 1913) found that the diazomethyl ketone (I) derived from *O*-acetylmandelyl chloride behaved anomalously when treated with various acids, and neither 1 : 3-dihydroxy-1-phenylacetone (II) nor its 1-*O*-acetyl derivative (III) was obtained by these authors. 1 : 3-Dihydroxy-1-phenylacetone (II) has been mentioned without details in a patent (U.S.P. 2,043,950/1936), but, in view of the work of Bradley and Eaton and that to be described below, it is unlikely that free dihydroxyphenylacetone has been prepared or, indeed, that it is capable of other than transient existence.*

Bradley and Eaton stated that the diazomethyl ketone (I) in dilute sulphuric acid gave benzylglyoxal (IV) as the only crystalline reaction product, while benzaldehyde (identified as the 2 : 4-dinitrophenylhydrazone) was also produced. The chloromethyl ketone (V), on the other hand, they found to react with methyl-alcoholic sodium acetate to give 1-phenylpropane-1 : 2-dione (VI); benzoic acid was also isolated and doubtless originated by slow decomposition of (VI) (cf. Müller and von Pechmann, *Ber.*, 1889, **22**, 2127). Except when it was carefully purified, decomposition of the chloromethyl ketone (V) to (VI) occurred on storage. Although Bradley and Eaton stated, without details, that the diazo-ketone (I) " did not react easily with acetic acid," we readily effected this reaction, noted

* [*Added in proof, December 18th*, 1951.] Since this paper was written, Smith and Anderson (*J. Org. Chem.*, 1951, **16**, 963) have described the successful preparation of phenyldihydroxyacetone, m. p. 71—73°, by deacetylation of the diacetate at 0° with aqueous barium hydroxide, and note its ready transformation into (VI); we had made several tentative attempts to effect the deacetylation of (VII), at room temperature with methanolic sodium methoxide or with methanol containing a trace of hydrogen chloride without, however, achieving a satisfactory result.

the production of traces of the diketone (VI), and isolated 1 : 3-diacetoxy-1-phenylacetone (VII) and a substance $C_{10}H_{10}O_3$ (see below) possessing one acetyl group.

We found the chloro-ketone (V) to react with sodium acetate, in acetic acid containing acetic anhydride (*i.e.*, in an anhydrous medium), to give the diketone (VI), a fraction "b" corresponding in properties with the substance $C_{10}H_{10}O_3$, and 1 : 3-diacetoxy-1-phenylacetone (VII), which appears to be stable indefinitely at room temperature. Immediately after collection, fraction "b" had an odour of formaldehyde. Fraction "b" itself had strong reducing properties and gave with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid a dinitrophenylhydrazone, m. p. 134—136·5°, corresponding to a carbonyl compound $C_{10}H_{10}O_3$, and, in smaller amount, a second derivative, m. p. 179—184°, which appeared to correspond to a carbonyl compound $C_8H_8O_2$. The detection of formaldehyde, the composition of the substance, and the analytical data for the two 2 : 4-dinitrophenylhydrazones allow one to conclude that the compound $C_{10}H_{10}O_3$ was *O*-acetylmandelaldehyde (VIII) of which the dinitrophenylhydrazone, m. p. 134—136·5°, was a derivative; the somewhat impure dinitrophenylhydrazone, m. p. 179—184°, was probably crude mandelaldehyde (IX) 2 : 4-dinitrophenylhydrazone and was distinct from the 2 : 4-dinitrophenylhydrazone of benzoylcarbinol (X).



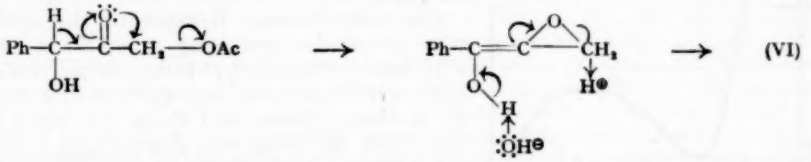
The formation of *O*-acetylmandelaldehyde (VIII) and formaldehyde from what had initially been 1 : 3-diacetoxy-1-phenylacetone (VII) requires the reasonable assumption that the 3-acetoxy-group had been hydrolysed during working-up of the mixture with sodium hydrogen carbonate with production of 1-acetoxy-3-hydroxy-1-phenylacetone (III). The facile decomposition of (III) to (VIII) and formaldehyde is analogous with the reversibility of the benzoin condensation (Lachman, *J. Amer. Chem. Soc.*, 1924, **46**, 708; cf. Buck and Ide, *ibid.*, 1931, **53**, 2350, 2784), the thermal decomposition of acetol to acetaldehyde and formaldehyde (Nef, *Annalen*, 1904, **335**, 250; Urion, *Compt. rend.*, 1932, **194**, 2145), and the more facile cleavage of benzoylcarbinol (X) to benzaldehyde (Zincke, *Annalen*, 1883, **216**, 286), although formaldehyde has not been detected in the last decomposition. Although mandelaldehyde (IX) has only been described once (Rinkes, *Rec. Trav. chim.*, 1920, **39**, 709) and earlier experiments designed to produce it gave, instead, benzoylcarbinol (X) (Evans and Parkinson, *J. Amer. Chem. Soc.*, 1913, **35**, 1772) the acetate (VIII) may have been obtained by Nef (*loc. cit.*, p. 268), and it yielded benzoylcarbinol (X) instead of (IX) on hydrolysis. The formation of benzaldehyde, noted by Bradley and Eaton, and the other observed transformations, for which valid analogies have been noted above, may therefore be summarised in the above scheme.

As it was obviously of interest, 3-acetoxy-1-hydroxy-1-phenylacetone (XI) was sought by way of the 1-benzyloxycarbonyl derivative (XII). Methoxycarbonylation of mandelic acid was described by Fischer and Fischer (*Ber.*, 1913, **46**, 2659) but their technique was not satisfactory when applied to benzyl chloroformate and mandelic acid; at a low temperature, however, methyl mandelate was converted in good yield to methyl *O*-benzyloxycarbonylmandelate by the action of benzyl chloroformate in the presence of a minimal amount of

pyridine, notwithstanding the decomposition of the acid chloride in the presence of pyridine expected as a side reaction (cf. Carré and Passedouet, *Compt. rend.*, 1935, **200**, 1767). The benzyloxycarbonyl group was extremely sensitive to cold methanolic potassium hydroxide, which gave a mixture of mandelic acid and methyl mandelate (cf. Fischer and Fischer, *loc. cit.*), but acid hydrolysis afforded *O*-benzyloxycarbonylmandelic acid in good yield. Conversion into the acid chloride and the diazo-ketone proceeded normally, and reaction of the latter with acetic acid readily gave (XII). Hydrogenolysis of this proceeded smoothly but the resulting monoacetate (XI), which was characterised as a semicarbazone, could not be crystallised and, on attempted distillation in a high vacuum, decomposed to give the diketone (VI) in good yield; similar decomposition also took place on storage.

(XI) HO·CHPh·CO·CH_2·OAc $\qquad$ CH_2Ph·O·CO·O·CHPh·CO·CH_2·OAc (XII)

The formation of 1-phenylpropane-1 : 2-dione (VI), and also of benzylglyoxal (IV) as observed by Bradley and Eaton, from dihydroxyphenylacetone derivatives is analogous with the well-known transformation of dihydroxyacetone into methylglyoxal (cf., *e.g.*, Bernier and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 1381). Exemplified by the present instance, the reaction may be interpreted as :

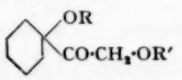


In this the initial stage is reminiscent of Ingold and Shoppee's generalised scheme for the pinacolin and related transformations (*J.*, 1928, 371) :

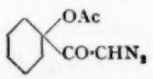
The first phase is presumably formation of the carbanion (XIII) and not the carbonium ion (XIV).

(XIII) HO·$\overset{\ominus}{C}$Ph·CO·CH_2·OAc $\qquad$ HO·CHPh·CO·$\overset{\oplus}{C}H_2$ (XIV)

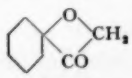
The synthesis of 1-acetoxyacetyl*cyclo*hexyl acetate (XV; R = R′ = Ac) from 1-hydroxy*cyclo*hexanecarboxylic acid proceeded smoothly and, since our work was concluded, a similar synthesis has been intimated by Alexander, Cocker, Cocker, and Lipman (*Chem. and Ind.*, 1951, 112). Hydrolysis of (XV; R = R′ = Ac) with potassium hydrogen carbonate yielded 1-hydroxyacetyl*cyclo*hexan-1-ol (XV; R = R′ = H) in excellent yield, compared with the less satisfactory conversion of 1-bromoacetyl*cyclo*hexyl bromide into (XV; R = R′ = H) (Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1873). Hydrolysis of (XV; R = R′ = Ac) with methanolic sodium methoxide was abnormal and the only identifiable products were *cyclo*hexanone and 1-hydroxy*cyclo*hexanecarboxylic acid.



(XV)



(XVI)

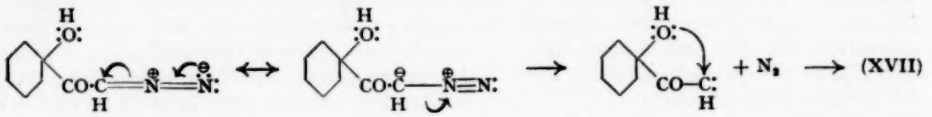


(XVII)

Hydrolysis of the crude diazo-ketone (XVI) with methanolic potassium hydroxide and treatment of the product with acetic acid gave the novel *spiro*-compound, 1-oxa*spiro*[3 : 5]-nonan-3-one (XVII), with only a small proportion of the expected product (XV; R = H, R′ = Ac). which has since been prepared by Billimoria and Maclagan (*Nature*, 1951, **167**, 81*) by the action of silver acetate on 1-bromoacetyl*cyclo*hexan-1-ol. The formation of (XVII) requires decomposition of the hydrolysed diazo-ketone to take place yielding a carbon atom with a sextet of electrons, the deficiency being made good by the oxygen

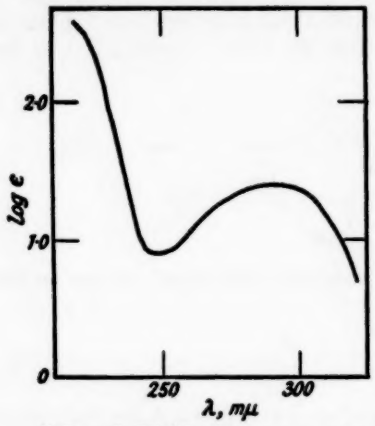
* Also *J.*, 1951, 3067.

atom of the alcoholic hydroxyl group presenting a pair of its unshared electrons to this carbon atom with migration of the proton. Analogies for this reaction, with formation of 5-membered heterocyclic rings, are the formation of the coumaranones (XVIII, XIX) by



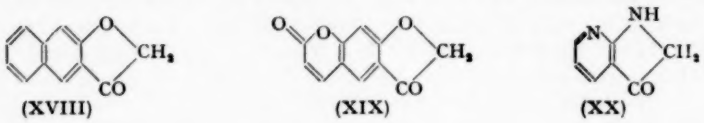
the action of acids on 3-diazoacetyl-2-naphthol (Krzikalla and Eistert, *J. pr. Chem.*, 1935, **143**, 50) and 6-diazoacetylumbelliferone propionate (von Bruchhausen and Hoffmann, *Ber.*, 1941, **74**, 1584) respectively; coumaranone itself is obtained in excellent yield from *o*-anisoyldiazomethane (Marshall, Kuck, and Elderfield, *J. Org. Chem.*, 1942, **7**, 444; Pfeiffer and Enders, *Chem. Ber.*, 1951, **84**, 247), and 7-pyrindoxyl (XXI) is produced as an intermediate from 2-amino-3-diazoacetylpyridine (Kägi, *Helv. Chim. Acta*, 1941, **24**, 141E).

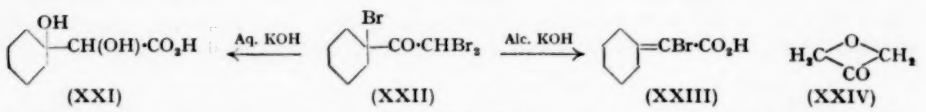
Light absorption of 1-oxaspiro[3 : 5]nonan-3-one in hexane.



The only previous instance of the deliberate removal of the protecting group in a blocked α′-hydroxy-α-diazomethyl ketone *before* transformation of the diazo-group appears to be that described by Wolfrom, Brown, and Evans (*J. Amer. Chem. Soc.*, 1943, **65**, 1025) who deacetylated 1-deoxy-1-diazo-*keto*-D-galaheptulose penta-acetate with methanolic ammonia before reaction of the resulting 1-deoxy-1-diazo-D-galaheptulose with formic acid, which gave an unidentified product and not, apparently, D-galaheptulose; it now appears that their material may have analogously contained a 5-membered ring.

Although Wolff rearrangement could conceivably have given the isomeric β-lactone * of 1-hydroxy*cyclo*hexylacetic acid, the structure of (XVII) followed from the typically ketonic ultra-violet light absorption (see figure) and from oxidative experiments (see p. 474). For example, alkaline hypoiodite gave, in small yield, 1-hydroxy*cyclo*hexylglycollic acid





(XXI), implying substitution in the methylene group and rearrangement of the Favorski type (*Bull. Soc. chim.*, 1926, **39**, 216) to the α-hydroxy-β-lactone as intermediate stages. An authentic specimen of (XXI) was obtained by brominating hexahydroacetophenone and treating the resulting tribromo-derivative (XXII) with aqueous potassium hydroxide following Favorski's method for the preparation of ββ-dimethylglyceric acid from methyl *iso*propyl ketone (*J. pr. Chem.*, 1913, **88**, 693), while it is noteworthy that the use of alcoholic potassium hydroxide afforded α-bromo*cyclo*hexylideneacetic acid (XXIII) (Wagner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 3655).

* This structure is erroneously ascribed by the " Ring Index " (no. 556; p. 99) to what is really the γ-lactone of *cyclo*hexanol-2-acetic acid (von Braun and Münch, *Annalen*, 1928, **465**, 61).

The substance (XVII) was acidic (pK_a ~12·5) and dissolved readily in aqueous alkali, being reprecipitated unchanged by carbon dioxide; in these respects its behaviour was reminiscent of that of coumaranone (cf. Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1081) but its reducing action on Fehling's solution and ammoniacal silver nitrate appeared to be much weaker. In an attempt to prepare the parent compound, oxetan-3-one (XXIV), chloroacetyl chloride was treated with diazomethane and the crude chloroacetyldiazomethane was hydrolysed with aqueous methanolic potassium carbonate. Reaction with acetic acid and fractionation then afforded ketonic material distilling below the b. p. of acetic acid and giving a 2 : 4-dinitrophenylhydrazone of the composition expected for that of (XXIV).

We are indebted to our colleague Dr. D. A. Long for his kindness in examining (VII) and (XV; R = R′ = H) for any effect on the sensitivity of tuberculin-sensitized guinea pigs to tuberculin of the type shown by cortisone and A.C.T.H. (Long and Miles, *Lancet*, 1950, I, 492); neither substance had any action.

Experimental.

1 : 3-*Diacetoxy*-1-*phenylacetone* (VII).—(a) *Action of acetic acid on* O-*acetylmandelyldiazomethane.* *O*-Acetylmandelyl chloride (*Org. Synth.*, **4**, 1) (10 g.) in dry ether (40 c.c.) was added to a solution (dried for 3 hours over potassium hydroxide pellets) of diazomethane (4·2 g.) in dry ether (380 c.c.). Next morning part of the ether was removed to demonstrate the presence of excess of diazomethane. After the addition of glacial acetic acid (25 c.c.) the remainder of the ether was removed and the residual orange liquid was heated on the boiling water-bath for 1½ hours. The mixture was then treated with aqueous sodium hydrogen carbonate to pH 8, and the product was recovered in ether as a brown syrup (11·6 g.). Fractionation afforded a yellow fore-running, presumably containing 1-phenylpropane-1 : 2-dione, followed by a viscous, slightly yellow syrup (8·1 g.), b.p. (mainly) 140—148°/1 mm. Fractionation yielded (i) a liquid, probably O-*acetylmandelaldehyde* (VIII), b. p. 95°/0·6 mm., n_D^{18} 1·5345 (Found: C, 67·6; H, 5·5; OAc, 26·3. $C_{10}H_{10}O_3$ requires C, 67·5; H, 5·6; OAc, 24·2%), and (ii) 1 : 3-*diacetoxy*-1-*phenylacetone* as a colourless liquid (3·2 g.), b. p. 110°/0·04 mm., n_D^{21} 1·5085 (Found: C, 62·8; H, 5·8; OAc, 37·0. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6; OAc, 34·4%).

The acetyl determinations were carried out in the apparatus described by Clark (*Ind. Eng. Chem., Anal.*, 1936, **8**, 487), and occasional somewhat high values found are attributable to the production, besides acetic acid, of traces of acidic by-products appreciably volatile in steam; in the above cases the formation of traces of benzoic acid is probable.

(b) *Reaction between* α-*acetoxybenzyl chloromethyl ketone* (V) *and sodium acetate.* Anhydrous sodium acetate (15 g.) was heated under reflux for an hour with acetic anhydride (30 c.c.) and acetic acid (100 c.c.). After cooling, α-acetoxybenzyl chloromethyl ketone (Bradley and Eaton, *loc. cit.*) (18·2 g.) was added, and the mixture was heated on the water-bath for 3 hours, sodium chloride being precipitated. The solvent was removed as far as possible in a vacuum and the residue was distributed between ether and water. Fractionation of the dried ethereal extract afforded (*a*) a yellow fore-running (2 g.), (*b*) a nearly colourless fraction (8 g.), b. p. 83°/0·1 mm., n_D^{20} 1·5339, corresponding with fraction (i) of the previous experiment, (*c*) an intermediate fraction (3 g.), and (*d*) 1 : 3-diacetoxy-1-phenylacetone (2 g.) as a viscous colourless syrup, apparently stable indefinitely at room temperature, b.p. 105—110°/0·03 mm., n_D^{20} 1·5151 (Found: C, 62·2; H, 5·6; OAc, 34·9%).

Fraction (*a*) was distributed between ether and aqueous sodium hydrogen carbonate solution, the latter yielding benzoic acid on acidification. The ethereal solution yielded 1-phenylpropane-1 : 2-dione (0·54 g.) which, on treatment with *o*-phenylenediamine (0·39 g.) in hot acetic acid (5 c.c.), afforded 2-methyl-3-phenylquinoxaline (0·6 g.), m. p. 56—59°, after distillation at 120—130°/0·002 mm. and recrystallisation from light petroleum (lit., m. p. 57—58°) (Found: N, 13·1. Calc. for $C_{15}H_{12}N_2$: N, 12·7%).

Immediately after distillation, fraction (*b*) had an odour of formaldehyde, the presence of which was confirmed by the reddish-brown colour given by the vapours with benzene and concentrated sulphuric acid on a glass rod. The product reduced Fehling's solution and ammoniacal silver nitrate readily in the cold. It gave a gummy semicarbazone. The product obtained from this fraction (0·46 g.) and 2 : 4-dinitrophenylhydrazine (0·35 g.) in cold ethyl alcoholic sulphuric acid contained at least three compounds. After rejection of a sparingly soluble and relatively high-melting substance, fractional crystallisation from alcohol afforded

O-*acetylmandelaldehyde* 2 : 4-*dinitrophenylhydrazone* as orange-yellow flattened needles, m. p. 134—136·5° (Found: C, 55·8; H, 3·7; N, 16·4. $C_{16}H_{14}O_6N_4$ requires C, 55·3; H, 4·0; N, 16·1%); successful separation of this material depended on rapid collection of the crystals by centrifugal filtration a few minutes after crystallisation from the hot solution had set in. After evaporation of pooled mother-liquors, crystallisation of the residue from alcohol gave orange-yellow plates, m. p. 179—184°, probably essentially mandelaldehyde 2 : 4-dinitrophenylhydrazone (Found: C, 52·2; H, 3·2; N, 19·0. Calc. for $C_{14}H_{12}O_5N_4$: C, 53·1; H, 3·8; N, 17·7%).

Attempted Alkaline Hydrolysis of O-*Acetylmandelyldiazomethane.*—The diazoketone (from 12 g. of *O*-acetylmandelyl chloride) was treated with a cold solution of potassium hydroxide (10 g.) in methanol (200 c.c.). The solution rapidly became dark reddish-brown and effervescence took place for about 10 minutes. Slight evolution of heat was controlled by external cooling. After 3 hours, water (200 c.c.) was added and the methanol was removed at 40° under reduced pressure. A small amount of neutral material was extracted with ether. On acidification of the aqueous solution a brown syrup (7 g.) was obtained by extraction with ethyl acetate. Sublimation of part of this product at 120—125°/25 mm. showed it to consist largely of benzoic acid, m. p. and mixed m. p. 123° (Found: C, 68·8; H, 5·3. Calc. for $C_7H_6O_2$: C, 68·8; H, 4·9%); no other identifiable product was isolated.

Methyl O-*Benzyloxycarbonylmandelate.*—Benzyl chloroformate (*Org. Synth.*, **23**, 13) (45 c.c.) was added dropwise during 2 hours to a vigorously stirred mixture of methyl mandelate (32·4 g.) and dry pyridine (25 c.c.), cooled to 0°. Stirring was continued for a further hour. On the following day, the semi-solid orange-brown mixture was treated with 3N-hydrochloric acid (125 c.c.) and extracted with ether. The residue after removal of the ether was heated to 165°/0·7—1·0 mm. to remove any benzyl chloride and methyl mandelate. The resulting product was poured into methanol (150—200 c.c.), and the solution was cooled to 0°, whereupon *methyl* O-*benzyloxycarbonylmandelate* (43·7 g., 75%) crystallised in stout colourless needles, m. p. 48° (Found: C, 67·7; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). The yield was reduced to 55% when a greater proportion of pyridine was used and was not improved by carrying out the reaction at −30°.

The acidic washings were basified and exhaustively extracted with ether. The aqueous solution was then acidified with hydrochloric acid and evaporated as far as possible, yielding a syrup. On treatment with mercuric chloride a portion of this syrup afforded 1-benzylpyridinium mercurichloride, which separated from water in colourless plates, m. p. 85—87° after desiccation; Ferns and Lapworth (*J.*, 1912, **101**, 283) record m. p. 86—89°. Another portion of the syrup yielded with aqueous sodium picrate an oily picrate, which slowly crystallised; recrystallisation from alcohol gave orange prisms of 1-*benzylpyridinium picrate*, m. p. 116—118° (Found: C, 54·1; H, 3·2; N, 13·9. $C_{18}H_{14}O_7N_4$ requires C, 54·3; H, 3·5; N, 14·1%).

O-*Benzyloxycarbonylmandelic Acid.*—A mixture of the above methyl ester (48 g.), acetic acid (192 c.c.), and concentrated hydrochloric acid (16 c.c.) was kept at 37° for 14 hours, during which there was a slight evolution of carbon dioxide without obvious effervescence. The solvent was removed in a vacuum at 40° as far as possible and the residue was treated with excess of dilute aqueous sodium hydrogen carbonate. Extraction with ether afforded essentially unchanged starting material (20 g.). The aqueous phase was acidified to pH 2 and extracted with ether. The residue left on removal of the ether was washed with water to remove traces of mandelic acid and dried, affording pure O-*benzyloxycarbonylmandelic acid* (24 g.; 53%, or 87% on amount hydrolysed), m. p. 123—125° (Found: C, 67·3; H, 5·2. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

The acid is readily soluble in methanol, ethyl acetate, and ether, soluble in benzene, but sparingly soluble in water and ligroin. It is best recrystallised from 50% acetic acid from which it separates in colourless needles.

O-*Benzyloxycarbonylmandelyldiazomethane.*—The acid chloride, prepared from the foregoing acid (24 g.) and thionyl chloride (60 c.c.) on the water-bath and freed from excess of thionyl chloride in a vacuum at 100°, was dissolved in dry ether (150 c.c.) and added to a solution of diazomethane (from 41 g. of nitrosomethylurea) in dry ether (400 c.c.) with continual shaking. The product crystallised rapidly. Next day the substance (16·5 g., 63%) was collected and washed with ether, only traces remaining in the mother-liquors and washings. Recrystallisation from ethyl acetate or, better, from methanol gave pale yellow prisms of O-*benzyloxycarbonylmandelyldiazomethane*, m. p. 121° (Found: C, 65·6; H, 4·7; N, 9·3. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·5; N, 9·0%).

3-*Acetoxy*-1-*benzyloxycarbonyloxy*-1-*phenylacetone* (XII).—A solution of the preceding diazoketone (3·7 g.) in glacial acetic acid (20 c.c.) was heated on the water-bath for 2½ hours. The

excess of acetic acid was removed in a vacuum and crystallisation of the residue from methanol (20 c.c.) afforded colourless prisms of **3-*acetoxy*-1-*benzyloxycarbonyloxy*-1-*phenylacetone*** (2·9 g., 71%), m. p. 78·5—80° (Found: C, 66·3; H, 5·2; OAc, 13·4. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3; OAc, 12·6%).

3-*Acetoxy*-1-*hydroxy*-1-*phenylacetone Semicarbazone*.—The above ketone (1·2 g.) in methanol (25 c.c.) was shaken with palladised charcoal (0·2 g.) in a stream of hydrogen. Evolution of carbon dioxide ceased after 40—45 minutes and the reaction was stopped after 50 minutes. After removal of the catalyst, removal of the solvent in a vacuum at 30—40° left a viscous colourless syrup, which was treated with semicarbazide hydrochloride (0·42 g.) and sodium acetate (0·35 g.) in water with addition of methanol to homogeneity. After being kept overnight the methanol was partly removed and addition of water precipitated **3-*acetoxy*-1-*hydroxy*-1-*phenylacetone semicarbazone*** (0·65 g.), which separated from aqueous methanol in colourless elongated prisms, m. p. 133° (Found: C, 54·2; H, 5·7; N, 15·4. $C_{12}H_{15}O_4N_3$ requires C, 54·4; H, 5·8; N, 15·8%).

In further experiments, all attempts to crystallise the parent ketone (XI) failed. It was converted in good yield into 1-phenylpropane-1 : 2-dione, b. p. 65°/0·3 mm., on attempted distillation in a high vacuum at 100°. The ketone also became bright yellow and acquired the odour of the diketone when kept.

1-*Acetoxy*cyclo*hexanecarbonyl Chloride*.—1-Acetoxy*cyclo*hexanecarboxylic acid (Bucherer and Dahlem, *J. pr. Chem.*, 1934, **140**, 251) (56 g.) was refluxed with thionyl chloride (70 c.c.) on the boiling water-bath for 10 minutes, a reddish-brown colour developing. The excess of thionyl chloride was removed in a vacuum and colourless 1-acetoxy*cyclo*hexanecarbonyl chloride (49 g., 84%) passed over at 87°/1·4 mm. (Found: C, 52·9; H, 6·4. Calc. for $C_9H_{13}O_3Cl$: C, 52·8; H, 6·4%). Alexander *et al.* (*loc. cit.*) record b. p. 121°/18 mm.

No advantage was gained by the use of pyridine in ether (cf. Carré and Libermann, *Compt. rend.*, 1934, **199**, 1422), and, in the above experiment, the yield was considerably reduced when the time of reflux exceeded 10 minutes.

1-*Acetoxyacetyl*cyclo*hexyl Acetate* (XV; R = R′ = Ac).—The above acid chloride (15 g.) in dry ether was added during 5 minutes to a dried ethereal solution of diazomethane (from 41 g. of nitrosomethylurea) in the usual manner. The following day the ether was removed, glacial acetic acid (25 c.c.) was added, and the mixture was heated on the water-bath for an hour. Lest any of the chloromethyl ketone should have been present, heating was continued for 2½ hours after the addition of anhydrous sodium acetate (3 g.). The crude product (17 g.) was isolated by neutralisation with sodium hydrogen carbonate and extraction with ether. A preliminary distillation at 1·2 mm. freed the product from 20—30% of a dark still residue and fractionation of the distillate afforded 1-acetoxyacetyl*cyclo*hexyl acetate in good yield as a colourless liquid, b. p. 117·5—119°/0·3 mm., n_D^{20} 1·4710 (Found: C, 59·4; H, 7·8; OAc, 32·8. Calc. for $C_{12}H_{18}O_5$: C, 59·5; H, 7·5; OAc, 35·5%). The low acetyl value may be attributable to some deacetylation by the action of the sodium hydrogen carbonate occurring during working up (cf. following experiment). Alexander *et al.* (*loc. cit.*) record b. p. 165°/18 mm.

1-*Hydroxyacetyl*cyclo*hexanol* (XV; R = R′ = H).—Potassium hydrogen carbonate (3·0 g.) was added to 1-acetoxyacetyl*cyclo*hexyl acetate (1 g.) in methanol (15 c.c.), and the mixture was left for 48 hours. Addition of water and extraction (thrice) with ether yielded a colourless syrup (0·61 g.) with a slight odour of *cyclo*hexanone. Recrystallisation from benzene afforded colourless prisms (0·51 g., 85%) of 1-hydroxyacetyl*cyclo*hexanol, m. p. 87—89·5° (Found: C, 61·3; H, 8·9. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%). Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) record m. p. 86—87°.

The substance rapidly reduced Fehling's solution and ammoniacal silver nitrate in the cold.

Hydrolysis of **1-*Acetoxyacetyl*cyclo*hexyl Acetate with Sodium Methoxide*.**—1-Acetoxyacetyl-*cyclo*hexyl acetate (0·73 g.) was treated with dry methanol (10 c.c.) containing sodium methoxide (from 0·1 g. of sodium). After 24 hours, the orange solution was diluted with water, saturated with carbon dioxide, and extracted with ether. The product (0·26 g.) would not crystallise from benzene, indicating non-identity with the foregoing 1-hydroxyacetyl*cyclo*hexanol. The presence of *cyclo*hexanone was established by distillation and preparation of the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 162°. Acidification of the alkaline aqueous layer to Congo-red and extraction with ether afforded a gum which subsequently crystallised, the solid being identified as 1-hydroxy*cyclo*hexanecarboxylic acid, m.p. and mixed m. p. 107°.

1-*Oxa*spiro[3 : 5]*nonan*-3-*one* (XVII) ***and*** **1-*Acetoxyacetyl*cyclo*hexanol*** (XV; R = H, R′ = Ac).—1-Acetoxy*cyclo*hexanecarbonyl chloride (25 g.) in dry ether was added to a dried solution of diazomethane (11 g.) in dry ether (420 c.c.). After being kept overnight the ether

and excess of diazomethane were removed on a water-bath at 50°. A chilled solution of potassium hydroxide (25 g.) in methanol (500 c.c.) was added to the cooled oily residue, and the solution became orange-coloured immediately. After 6 hours at room temperature, the orange-red solution was diluted with water (350 c.c.), and the methanol was removed in a vacuum at 30°. The filtered solution was exhaustively extracted with ether, and the extract dried (K_2CO_3) and evaporated at >50° on the water-bath, yielding a yellow oil (15 g.). Addition of glacial acetic acid (90 c.c.) produced effervescence and slight evolution of heat. The mixture was heated on the boiling water-bath for 2 hours, cooled, treated with excess of aqueous sodium hydrogen carbonate, and thoroughly extracted with ether. Fractionation of the dried extract yielded (i) 1-*oxa*spiro[3 : 5]*nonan*-3-*one* (XVII) (see below) (8·5 g., 49% based on the acid chloride) having a camphoraceous odour, b. p. 86°/28 mm., n_D^{19} 1·4631, absorption max. in hexane 290 mμ (log ε = 1·4) (Found : C, 68·5; H, 8·9. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%), and (ii) 1-acetoxyacetyl*cyclo*hexanol (XV; R = H, R′ = Ac) as a colourless oil (1·5 g.), b. p. 126—133°/1·5 mm., 118—124°/0·6 mm. (Found : C, 60·3; H, 7·9; OAc, 23·2. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0; OAc, 21·5%). Billimoria and Maclagan (*loc. cit.*) record b. p. 90—92°/10^{-6} mm., m. p. 42—43°. The semicarbazone crystallised from aqueous alcohol in colourless needles, m. p. 163—168° (Found : C, 51·5; H, 7·3; N, 16·5. Calc. for $C_{11}H_{19}O_4N_3$: C, 51·4; H, 7·4; N, 16·4%). Billimoria and Maclagan (*loc. cit.*) record m. p. 172—173°.

When kept for several months 1-oxa*spiro*[3 : 5]nonan-3-one gradually deteriorated and quantitative recovery was not possible on redistillation. The substance was sparingly soluble in water but readily soluble in 2N-sodium hydroxide, being reprecipitated therefrom by carbon dioxide. A solution of the substance (3·95 g.) in cold 2N-sodium hydroxide (50 c.c.) was set aside at room temperature for 24 hours. Acidification, extraction with ether, and fractionation afforded unchanged material (3 g.), b. p. 76°/22 mm., n_D^{19} 1·4628, and a brown tarry still residue. Potentiometric titration using a lithium glass electrode indicated a pK_a of ~12·5.

The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 165—167° (Found : C, 52·9; H, 4·9; N, 17·6. $C_{14}H_{16}O_5N_4$ requires C, 52·5; H, 5·0; N, 17·5%). The *semicarbazone* separated from alcohol in colourless prisms, m. p. 191—194° (Found : C, 54·9; H, 7·7; N, 21·8. $C_9H_{15}O_3N_3$ requires C, 54·9; H, 7·6; N, 21·3%).

Degradation of 1-*Oxa*spiro[3 : 5]*nonan*-3-*one*.—(a) *Oxidation to adipic acid.* Potassium permanganate (1·69 g.) was added gradually to a solution of the substance (0·50 g.) in water (15 c.c.) containing potassium hydroxide (0·3 g.), addition of the oxidising agent being stopped when the rate of oxidation became slow. Filtration, extraction with ether, acidification with hydrochloric acid, and further extraction with ether yielded adipic acid, m. p. and mixed m. p. 151°. Adipic acid was also isolated in small yield when a cold solution in 2N-sodium hydroxide was treated with 20-vol. hydrogen peroxide solution.

(b) *Oxidation to* 1-*hydroxy*cyclo*hexylglycollic acid* (XXI). Iodine (7·2 g., 4 at.) was added to a solution of the substance (2·0 g.) in water (80 c.c.) containing potassium hydroxide (4 g.), the mixture being shaken until all the iodine dissolved. On the following day, the pale yellow solution was extracted with ether, and then treated with 3N-hydrochloric acid (26 c.c.) and enough sodium metabisulphite to react with the iodine liberated. Extraction with ether gave a greenish-brown gum (0·63 g.), affording a crystalline solid (0·20 g.) on treatment with benzene. Crystallisation from benzene–ethyl acetate yielded colourless prisms, m. p. 117—119°, not depressed on admixture with authentic 1-*hydroxy*cyclo*hexylglycollic acid* (see below) (Found : C, 55·3; H, 8·3. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%). On treatment of the acid (43·5 mg.) in water (2 c.c.) with 0·5M-periodic acid (0·5 c.c.), the odour of *cyclo*hexanone developed rapidly. Next day the mixture was basified with sodium hydroxide and extracted with aldehyde-free ether. Treatment of the extract with Brady's reagent afforded *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 162° (Found : N, 19·8; Calc. for $C_{12}H_{14}O_4N_4$: N, 20·1%).

(c) *Oxidation to* 1-*hydroxy*cyclo*hexanecarboxylic acid.* A solution of benzenediazonium chloride [from aniline (0·67 g.), 3N-hydrochloric acid (5 c.c.), and sodium nitrite (0·5 g.)] was added to a solution of the substance (0·9 g.) in 2N-sodium hydroxide (15 c.c.) containing added potassium hydroxide (1·5 g.). The solution became dark reddish-brown and a small amount of a dark tar was precipitated. After half an hour, during which some nitrogen was evolved, the acidity was brought to 5N. by the addition of concentrated hydrochloric acid. The mixture was then heated on the water-bath for 3 hours. Extraction with ether yielded an oil (0·5 g.) distilling above 100°/0·002 mm. The distillate was separated into neutral and acidic fractions by partition between ether and dilute aqueous alkali. The acidic fraction, recovered by acidification and extraction with ether, was essentially 1-hydroxyl*cyclo*hexanecarboxylic acid, the product

obtained by recrystallisation from carbon tetrachloride and then from benzene having m. p. 107°, alone and in admixture with an authentic specimen (Found: C, 58·6; H, 8·3. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%). A small quantity was converted into the acetyl derivative which showed no depression in m. p. when mixed with an authentic specimen.

1-*Bromo*-1-*dibromoacetyl*cyclo*hexane* (XXII).—Bromine (38·5 g.) was added gradually in a slow stream of carbon dioxide to warm hexahydroacetophenone (10 g.). After the addition of the bromine the reaction was completed by ½ hour's heating on the water-bath. The tribromo-ketone solidified on cooling. Crystallisation from ligroin, with alumina treatment to remove coloured impurities, afforded colourless needles (20 g.), m. p. 74—76° (Found: C, 27·0; H, 3·1; Br, 66·4. Calc. for $C_8H_{11}OBr_3$: C, 26·5; H, 3·0; Br, 66·2%). Wagner and Moore (*loc. cit.*) record m. p. 72·5—74°.

1-*Hydroxy*cyclo*hexylglycollic Acid* (XXI).—The above tribromo-ketone (2·0 g.) was treated with potassium hydroxide (1·6 g.) in water (10 c.c.) and boiled until dissolution was complete. The solution was then strongly acidified and repeatedly extracted with ether. Removal of the ether from the dried extract yielded 1-hydroxy*cyclo*hexylacetic acid (0·21 g.), which separated from benzene in colourless prisms, m. p. 117° (Found: C, 55·5; H, 7·9%).

Oxetan-3-*one* 2 : 4-*Dinitrophenylhydrazone*.—Freshly distilled chloroacetyl chloride (5 c.c.), in dry ether, was added slowly to a dried solution of diazomethane (6 g.) in ether (390 c.c.). After being kept overnight, the ether and excess of diazomethane were removed in a vacuum at 50°, and the residue was treated in methanol (20 c.c.) with potassium carbonate (10 g.) and water (8 c.c.). The mixture was stirred from time to time during 4 hours, during which it became dark brown in colour and effervesced continually. The methanol was removed as far as possible in a vacuum at 50° and the residue was extracted twice with ether by stirring and decantation. Evaporation of the ethereal solution afforded a yellowish-brown syrup. This was treated with glacial acetic acid (10 c.c.) and the mixture was warmed under reflux until obvious reaction ceased. Thereafter the mixture was carefully fractionated through a 10-cm. fractionating column. Three fractions (each of 0·5—1 c.c.) were collected while the b. p. rose to that of acetic acid. When tested with 2 : 4-dinitrophenylhydrazine in ethanolic sulphuric acid, the first fraction gave a strongly positive test, the second a weakly positive, and the third a negative test. A control experiment with the acetic acid gave no sign of a ketonic fore-running. The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in pale orange-coloured flattened needles, m. p. 152—155° (Found: C, 42·7; H, 3·4. $C_9H_8O_5N_4$ requires C, 42·8; H, 3·2%).

A chloride ion determination on the spent potassium carbonate solution showed the presence of 75% of the amount calculated for formation and hydrolysis of chloroacetyldiazomethane.

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91. *The Infra-red Spectra of Some Organo-phosphorus Esters.*

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The infra-red spectra of 33 esters of phosphorus have been examined. Characteristic frequencies are suggested for the P–O–Ar (2) and the P–O–C (aliphatic) linkage. Frequencies already suggested for the P=O, P–H, P=S, and P–F links are discussed in the light of our findings.

Previous studies of the infra-red spectra of organo-phosphorus compounds have been few although this class of compound is of rapidly growing importance both on the commercial side—where they find applications as plasticisers, resins, lubricating oil additives, insecticides, etc.—and the biochemical side for studies on phosphate metabolism. In all these fields it is important to know whether characteristic frequencies exist, which can be correlated with the various units of molecular structure, and the primary aim of this work has been to examine as many compounds as possible from this point of view, although it was hoped that some data on the structure of the materials might be obtained at the same time. It will be appreciated that all the correlations suggested are liable to be affected by changes in the polarity or weight of the substituent groups, especially where skeletal vibrations are concerned, but they appear to show sufficient consistency to be likely to be of some value in structural diagnosis provided that the necessary caution is observed.

Previous work along these lines has been carried out by Meyrick and Thompson (*J.*, 1950, 225) who examined the infra-red and Raman spectra of some ten alkyl esters of phosphorus oxy-acids, and suggested correlations for the P=O, P–H, and P–O linkages; and after the completion of this work, Gore (Symposium of the Faraday Soc. on Spectrography and Molecular Structure, 1950, in the press) and Smith (*ibid.*) have also suggested a number of likely correlations. These will be discussed in the light of our own findings.

Experimental.—The compounds whose spectra have been measured were largely synthetic products prepared in these laboratories, although a few have been supplied by Dr. W. Gerrard, of Northern Polytechnic, and Dr. Kilby, of Leeds University. All were believed to be of reasonably high purity and the phosphorus content, refractive index, b. p. or m. p., etc., were checked in all cases.

The spectra were obtained by using the Perkin-Elmer 21B recording double-beam spectrometer with a rock-salt prism.

Liquid samples were examined as films pressed between rock-salt plates and/or as solutions in carbon disulphide. Solid samples were similarly examined by using the Nujol grinding technique and/or solution methods. All the solution studied were examined in the same amalgam-sealed cell 0·05 mm. thick at 5% concentration.

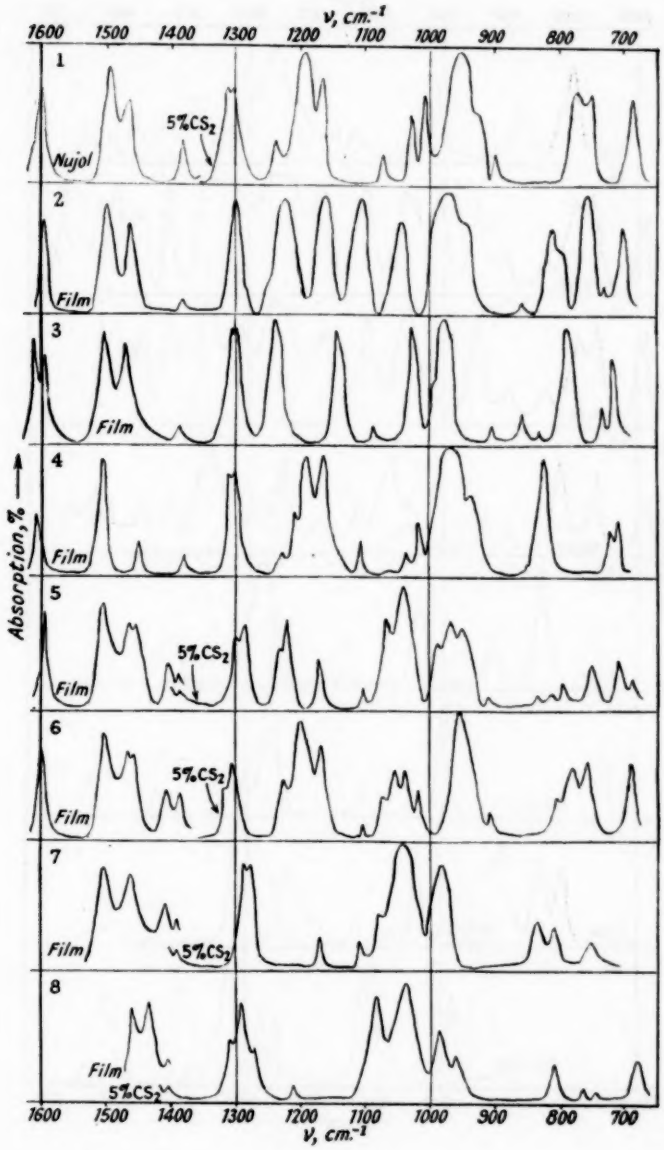
The P=O *Grouping.*—The position of this grouping is fairly well defined. Phosphorus oxychloride shows a strong band near 1274 cm.$^{-1}$ which is absent in phosphorus trichloride, and this band also appears in the Raman spectrum of the oxychloride, where it has been assigned to the P=O vibration. On this basis, Meyrick and Thompson (*loc. cit.*) have assigned a similar band which they find in five phosphonates to this vibration. This is strongly supported by our own findings (see Table), particularly in compounds in which the P=O is replaced by the P=S link when there is almost no alteration of spectra other than the disappearance of the 1280 cm.$^{-1}$ vibration. Gore (*loc. cit.*) has recently published data on some hundred phosphates and thiophosphates in which the same appearance and disappearance of this band with the P=O linkage are noted, and Smith (*loc. cit.*) has independently come to the same conclusion on other phosphates and phosphonates. There can therefore be little doubt of the validity of this assignment, although the limiting range in which the band can occur is rather more open. Thompson suggested 1250—1260 cm.$^{-1}$, which is obviously too narrow a range in the light of our results. Gore suggested 1250—1300 cm.$^{-1}$, and all our compounds run close to this range. Smith associates the position of the P=O link with the degree of electro-negativity of the substituents, as he finds considerable shifts when hydroxyl groups are present or when phenyl compounds are bonded directly to carbon. However, all his normal esters fall in the range 1250—1300 cm.$^{-1}$, as do our own, and this would be, therefore, the expected position of the P=O absorption, although it may be that it is liable to larger shifts in special circumstances.

The other point of interest in this connection is the doublet nature of the P=O vibration in many cases. Gore (*loc. cit.*) has suggested that this might arise from an O–C_2H_5 vibration close to that of the P=O itself. This will not explain the doublet character of this vibration in a number of fully aromatic compounds which we have prepared, although it may be the reason for the weaker absorption shown in this region by some of the alkyl phosphites and not shown by aromatic phosphites.

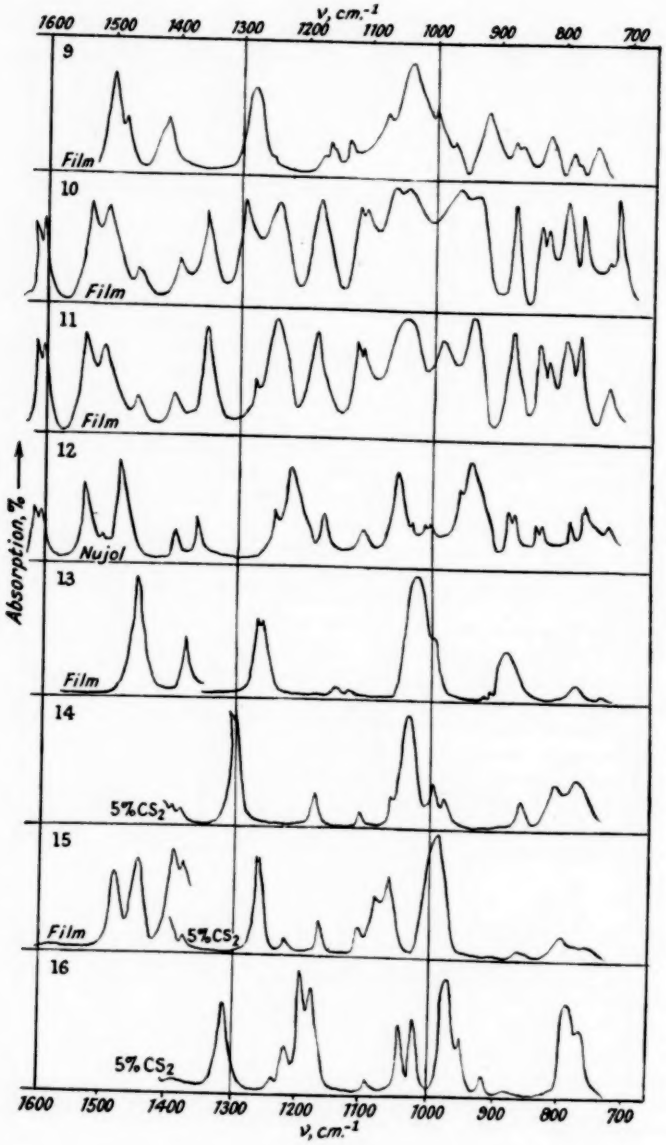
The P–O–C *Bond.*—The P–O–C bond might be expected to give rise to two characteristic frequencies, one arising from the P–O vibration, modified by the O–C link, and the other from the O–C linkage modified by the phosphorus atom. As skeletal vibrations they will be difficult to differentiate, as they are likely to occur in the wide regions of C–O or C–C stretching frequencies. However, the C–O–C– linkage gives rise to strong bands, so there is no reason to suppose that they will not arise with the P–O–C linkage also. By analogy with the carbon ether links it is to be expected that such characteristic bands would occupy different positions depending on whether the carbon atom is aromatic in nature or not.

(a) *The* P–O–C (*Aromatic*) *Linkage.*—A study of the spectra obtained shows that in all cases in which the P–O–C(Ar) grouping is present, an intense band appears in the region 1190—1240 cm.$^{-1}$. The figures obtained are indicated in the Table, and it will be seen from

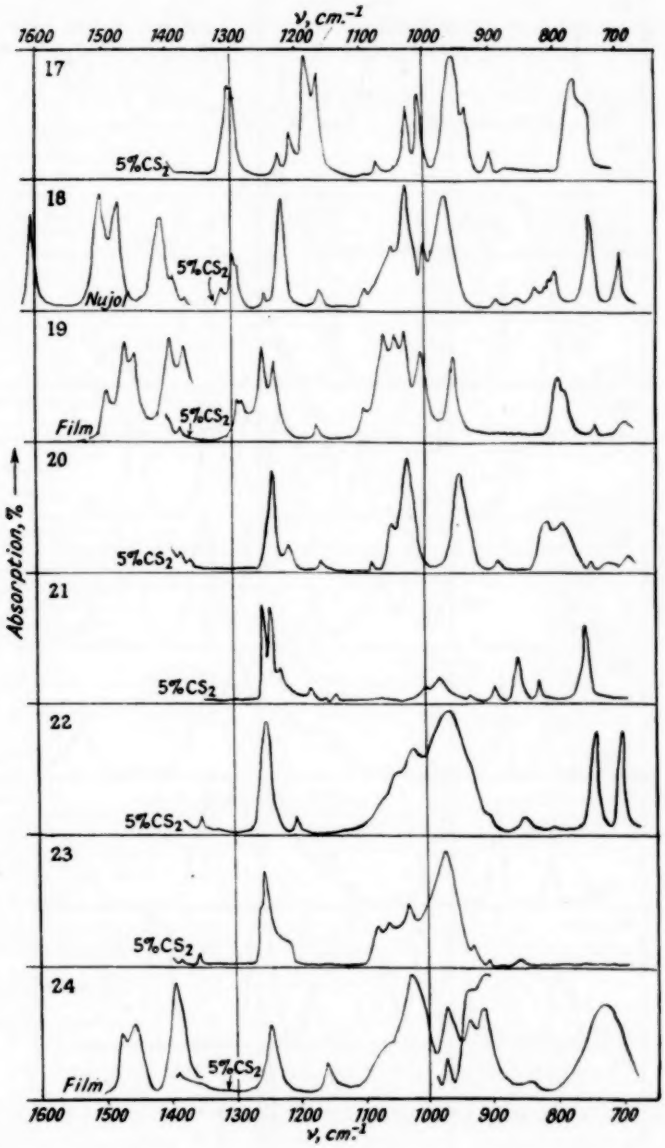
FIGS. 1—8.


ν, cm.⁻¹
1600 1500 1400 1300 1200 1100 1000 900 800 700
1
5% CS2
Nujol
2
Film
3
Film
4
Film
5
Film
5% CS2
6
Film
5% CS2
7
Film
5% CS2
8
Film
5% CS2
Absorption, % ⟶
1600 1500 1400 1300 1200 1100 1000 900 800 700
ν, cm.⁻¹

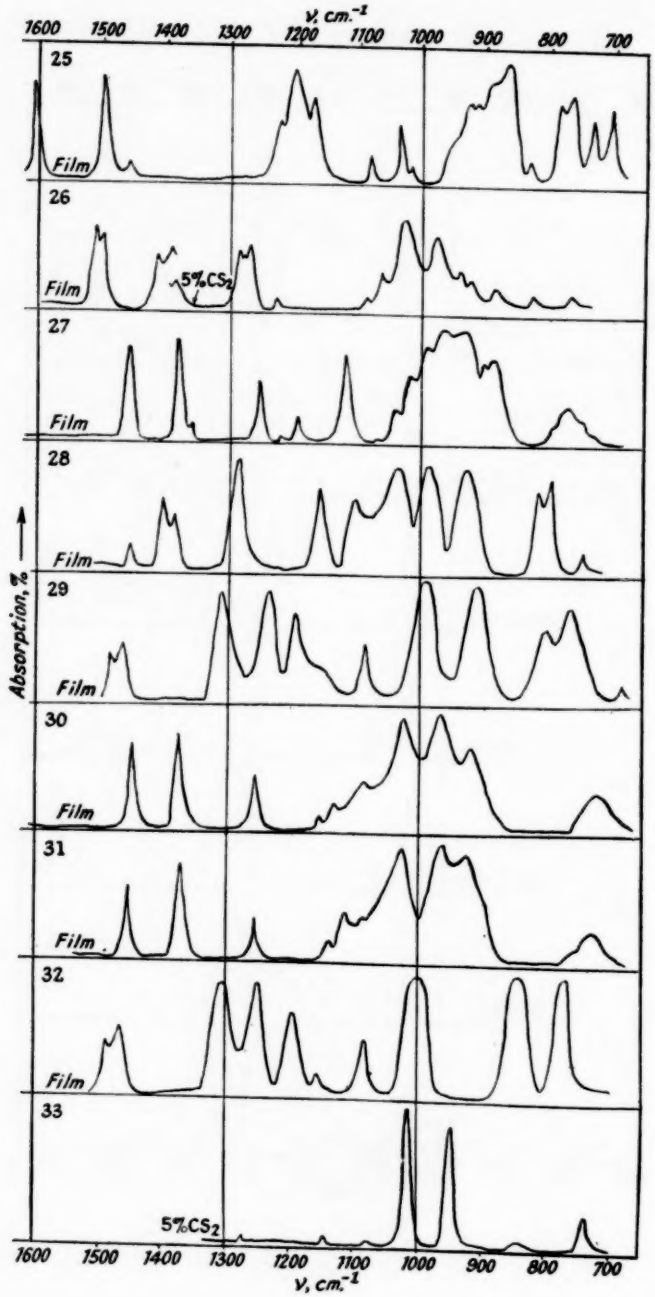
FIGS. 9—16.


ν, c.m.⁻¹
1600 1500 1400 1300 1200 1100 1000 900 800 700
9
Film
10
Film
11
Film
12
Nujol
13
Film
14
5% CS2
15
Film
5% CS2
16
5% CS2
Absorption, % →
1600 1500 1400 1300 1200 1100 1000 900 800 700
ν, c.m.⁻¹

FIGS. 17—24.


ν, cm.⁻¹
1600 1500 1400 1300 1200 1100 1000 900 800 700
17
5%CS₂
18
Nujol
5%CS₂
19
Film
5%CS₂
20
5%CS₂
21
5%CS₂
22
5%CS₂
23
5%CS₂
24
Film
5%CS₂
Absorption, %
1600 1500 1400 1300 1200 1100 1000 900 800 700
ν, cm.⁻¹

FIGS. 25—33.


ν, cm.⁻¹
1600 1500 1400 1300 1200 1100 1000 900 800 700
25
Film
26
Film
5% CS2
27
Film
28
Film
29
Film
30
Film
31
Film
32
Film
33
5% CS2
Absorption, % ⟶
1600 1500 1400 1300 1200 1100 1000 900 800 700
ν, cm.⁻¹

the spectra that compounds lacking the P–OAr group do not show this band. Dibenzyl phosphonate does not show more than a weak band in this region. Perhaps the strongest evidence for this assignment is given by the studies of a 5% solution in carbon disulphide of the related series triethyl phosphate, diethyl phenyl phosphate, ethyl diphenyl phosphate, and triphenyl phosphate. These were all measured in the same cell at the same concentration and it will be seen that this band is absent in the first and shows gradually increasing intensity throughout the series up to triphenyl phosphate. Similarly, there is

Compound	Fig. No.	Assignments made (band head position, cm.$^{-1}$) P–O–C (Aromatic)		P–O–C (Aliphatic)	P=O	Other assignments
Phosphates, etc.						
Triphenyl phosphate	1	1190	1029	—	1311 1299	—
Tri-*o*-tolyl phosphate	2	1220	1042	—	1299	—
Tri-*m*-tolyl phosphate	3	1242	1029	—	1307 1299	—
Tri-*p*-tolyl phosphate	4	1190	1022	—	1311 1297	—
Ethyl diphenyl phosphate	6	1192	1035	1046	1314 1297	—
Diethyl phenyl phosphate	5	1218	*	1037	1290 1279	—
Triethyl phosphate	7	—	—	1037	1280 1264	—
Tri-2-chloroethyl phosphate	8	—	—	1030	1282	—
Tributyl phosphate	9	—	—	1030	1274	—
Diethyl *p*-nitrophenyl phosphate	10	1232	*	1030	1282	—
Diethyl *p*-nitrophenyl thiophosphate	11	1232	*	1027	—	P=S, **763**, s.
Ethyl di-*p*-nitrophenyl thiophosphate	12	1205	*	1037	—	P=S, **766**, m.
Tri-2-ethylhexyl phosphate	13	—	—	1026	1282 1266	—
Phosphonates.						
Diethyl phosphonate	14	—	—	1053	1261	PH (unbonded), 2427
Diethyl chlorophosphonate	15	—	—	1030	1311	—
Diphenyl chlorophosphonate	17	1176	1027	—	1305 1297	—
Phenyl dichlorophosphinate	16	1186	1028	—	1305	—
Diethyl anilinophosphonate	18	—	—	1026	1290	—
Diethyl ethylphosphonate	19	—	—	1040 1025	1250	—
Diethyl butylphosphonate	20	—	—	1031	1242	—
*cyclo*Hexyldichlorophosphine oxide	21	—	—	1036 (weak)	1274 1258	—
Dibenzyl phosphonate	22	—	—	1031	1258	PH (unbonded), 2410
Di*neo*pentyl phosphonate	23	—	—	1026	1250	PH (unbonded), 2381
Phosphites.						
Triethyl phosphite	24	—	—	1030	—	Several of these show weaker absorption in the region of 1250
Triphenyl phosphite	25	1198	1026	—	—	
Tri*neo*pentyl phosphite	26	—	—	1022	—	
Tri-2-ethylhexyl phosphite	27	—	—	1031	—	
Ethyl di-2-ethylhexyl phosphite	31	—	—	1026	—	
Diethyl 2-ethylhexyl phosphite	30	—	—	1026	—	
Pyrophosphates, etc.						
Tetraethyl pyrophosphate	28	—	—	1030	1280	—
Bisdimethylaminophosphinic anhydride	29	—	—	—	1305	—
Bisdimethylaminofluorophosphine oxide	32	—	—	—	1305	P–F, 833
Ethyl dichlorophosphinate	33	—	—	1026	—	—

All the above are strong bands except where otherwise indicated.

* Denotes that band is obscured by that due to P–O–C(Alk.).

an increase in the intensity of this band on going from phenyl dichlorophosphinate to diphenyl chlorophosphonate to triphenyl phosphate. It is considered that this fact together with the evidence given in the Table, represents a strong case for this assignment, which is also supported by Gore's tentative suggestion (*loc. cit.*) that the P–O–Ph grouping may occur in the region 1200—1250 cm.$^{-1}$.

It is noteworthy that this frequency is within the region of the normal aromatic C–O–C assignment and may indicate that in fact the O–C stretching frequency is not materially

altered by the substitution of a phosphorus for a carbon atom. If this were to be the case, a second band of medium intensity in the range 1000—1060 cm.$^{-1}$, comparable with the second C–O–C band, might also be expected from the P–O–C (aromatic) link.

Further study of the spectra indicates that the aromatic esters show two sharp absorption bands at 1012 and 1030 cm.$^{-1}$ which undergo intensification with increase of aromatic content in related series. The first of these can be identified as being due to the aromatic ring itself, as it is displaced in *o*- or *p*-disubstituted compounds but not with *m*- or monosubstitution. It would therefore seem likely that the P–O–C (aromatic) linkage is responsible for the second band observed near 1030 cm.$^{-1}$. It is sometimes obscured by the intense P–O–C (aliphatic) absorption band (see below) but the differences in intensity are sufficient to avoid confusion between them.

(b) *The* P–O–C (*Aliphatic*) *Linkage.*—The occurrence of two bands assigned to P–O–C (aromatic) close to similar bands arising from the C–O–C (aromatic) grouping suggests that the P–O–C (aliphatic) bands might also occur in the 1000—1100-cm.$^{-1}$ region close to the C–O–C (aliphatic) vibrations, especially as the Si–O–C (aliphatic) band has also been found in the region close to the C–O–C position, indicating that the change of mass has not in this case markedly altered the frequency of the O–C vibration (Richards and Thompson, *J.*, 1949, 124).

Examination of the spectra shows that in all cases where the P–O–C (aliphatic) linkage is present (24 compounds) a very intense band occurs between 1030 and 1050 cm.$^{-1}$ which can be assigned to this link. As in the case just quoted, this band shows progressive changes in intensity as the number of alkyl groups is increased through a related series, and the band is absent from fully aromatic compounds. The actual band positions are indicated in the Table. The narrow range in which this band falls is remarkable for a skeletal vibration, and only slight shifts appear to be produced on alteration of the substituent groups through ethyl, butyl, *neo*pentyl, or 2-ethylhexyl or on changes in the substitution pattern through phosphates, phosphites, thiophosphates, phosphonates, etc.

The ten compounds examined by Meyrick and Thompson (*loc. cit.*) are in agreement with this assignment. These authors have tentatively suggested that absorption near 795 cm.$^{-1}$ may also be connected with the P–O–C linkage. The spectra which we have obtained bear out this suggestion to some extent, although we find the bulk of the band heads to be nearer 760 cm.$^{-1}$, and in this region we differ from their findings as regards the relative strengths of bands in two of the three compounds of theirs which we have re-examined. However, the bands in this region are usually broad, and are weak compared with those in the 1030—1050-cm.$^{-1}$ range. They also show large changes on solution in some cases, which suggests that they may arise from hydrogen-bonded linkages. They are therefore less likely to be of value in structural diagnosis work.

Other Assignments.—All the compounds examined were prepared with a view to working out the correlations given above, but some of them are also useful in providing a check—insofar as their numbers will allow—on other assignments proposed for this series.

(i) P–H. Meyrick and Thompson (*loc. cit.*) have given strong evidence for the assignment of the absorption band at 2300—2400 cm.$^{-1}$ to this group, and Smith (private communication) has confirmed this with seven other compounds. This is further supported by our spectra of dibenzyl phosphonate and di*neo*pentyl phosphonate which show a band in this region. This is also interesting in indicating that the existence of dialkyl hydrogen phosphite in the tautomeric phosphonate form is not confined to short-chain aliphatic materials. We have also re-examined the spectrum of diethyl phosphonate and differ from Meyrick and Thompson in that we find a sharp band at 2427 cm.$^{-1}$ in solution and in the liquid film, whereas they find a broad band in this region which they ascribe to hydrogen bonding. However, Kosolapoff and Powell (*J. Amer. Chem. Soc.*, 1950, **72**, 4291) have adduced from molecular weights that many dialkyl phosphites are monomeric and therefore unbonded.

(ii) P=S. Gore (*loc. cit.*) has found a weak band in many thiophosphates near 750 cm.$^{-1}$ which he ascribes to this linkage, and this has been confirmed by Smith (*loc. cit.*). We find both diethyl *p*-nitrophenyl thiophosphate and ethyl di-*p*-nitrophenyl thiophosphate to give absorption in this region.

(iii) P=F. Smith assigns this linkage to the region 750—900 cm.$^{-1}$. In a single compound, *viz.*, bisdimethylaminofluorophosphine oxide we find a very strong band at 833 cm.$^{-1}$ which is absent in the closely related bisdimethylaminophosphinic anhydride, and which may therefore be due to the P–F band.

We are indebted to Mr. E. F. Norman of this department for the preparation of the bulk of the compounds examined, and also to Drs. Carroll, Gerrard, and Kilby for gifts of samples. Thanks are also due to Mr. C. D'Oyly-Watkins for assistance with the practical work and to Dr. D. C. Smith for a very valuable discussion. We also thank the Chief Scientist, Ministry of Supply, for permission to publish the results.

MINISTRY OF SUPPLY, WOOLWICH ARSENAL. [*Received, August 24th,* 1951.]

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92. *Conjugation of a Hetero-atom across a Single Bond.*

By C. A. COULSON and J. DE HEER.

The molecular-orbital method is used to provide a general discussion of the way in which the conjugation of a hetero-atom (*e.g.*, a halogen) with a conjugated or aromatic hydrocarbon residue (*e.g.*, phenyl) depends on the electronegativity of the hetero-atom and the resonance integral between the hetero-atom and the carbon atom to which it is attached. This conjugation is shown to depend more strongly on the resonance integral than has often been supposed. The dependence is different according as we measure the extent of the conjugation in terms of delocalisation energy, bond order, or charge migration.

WHEN two conjugated systems AH and BH are joined together, as in Fig. 1, by elimination of the hydrogen atoms at *a* and *b*, we speak of an extended conjugation across the " single " bond *a*–*b*. In this process A and B may be hydrocarbon residues, such as phenyl groups giving diphenyl; or one of them may be a single atom with π-electrons available to extend the conjugation path previously limited to the other residue. An example of this type is a monosubstituted benzene, such as when A is phenyl and B is chlorine, giving chlorobenzene. In this latter case the chlorine atom contributes two electrons to the total conjugating system. If we adopt the molecular-orbital description of this phenomenon, we speak of a greater degree of delocalisation of the π-electrons; in the alternative valence-bond description we speak of the introduction of new " structures," in which the bond *a*–*b* appears double, and there may or may not be charges on some of the atoms of A and B. Conjugation of this kind should be reflected in (1) the bond order of the bond *a*–*b*, (2) the resonance energy, or (better) delocalisation energy, which results, and (3) the charge displacements associated with the final molecule, when compared with the composite parts, AH and BH.

FIG. 1.

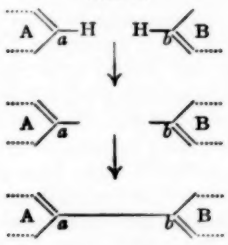
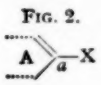


FIG. 2.



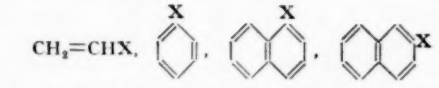
The situation in which A and B are alternant hydrocarbons has already been fairly fully discussed. Thus a large number of particular examples have been studied numerically by Coulson and Jacobs (*J.*, 1949, 1983) who showed that the larger the two residues, the

greater was the bond order of *a–b*. It has also been discussed theoretically by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1948, *A*, **195**, 188), who showed that if β_{ab} and p_{ab} are the resonance integral and π-bond order in the final bond *a–b*, and if R_{ab} is the conjugation energy across *a–b* (*i.e.* the extra delocalisation energy on forming A–B) then, in a close approximation :

$$R_{ab} \propto p_{ab} \cdot \beta_{ab} \propto \beta_{ab}^2 \times \sqrt{\pi_{a,a}} \times \sqrt{\pi_{b,b}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In this formula $\pi_{a,a}$ and $\pi_{b,b}$ are the self-polarisabilities of the centres *a* and *b* in the residues A and B, respectively (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 39). It was as a result of (1) that these authors identified $\pi_{a,a}$ and $\pi_{b,b}$ as the conjugating powers of A and B, though it now seems as if $\sqrt{\pi_{a,a}}$ would have been a better definition. In all this work the overlap integral between adjacent π atomic orbitals was tacitly neglected; but de Heer (*Phil. Mag.*, 1950, **41**, 370) showed that the result (1) was still substantially valid even when it was included, provided that the revised definitions of bond order, charge, and polarisability due to Chirgwin and Coulson (*Proc. Roy. Soc.*, 1950, *A*, **201**, 196) were used.

In all these discussions the two fragments A and B have been alternant hydrocarbons, so that there is no net flow of charge from A to B, or *vice versa*. One of our objects in this paper is to investigate this charge migration, and, in particular, to discover what factors (*e.g.* coulomb terms, resonance integrals, polarisabilities) are most effective in determining its magnitude. For this purpose we shall consider the case (Fig. 2) where A is an alternant hydrocarbon and B is a single hetero-atom, frequently a halogen. When B is a single atom it will be convenient to use a different symbol, and refer to it as X. We choose this type of molecule because it is amenable to theoretical treatment, and it is at the same time a prototype for all conjugation across a single bond involving at least one hetero-molecule. The applications of this study are quite numerous. Thus, on the one hand, by keeping X unchanged but by varying A, we discuss charge, bond order, and energy in a series such as type i, and, on the other hand, by keeping A unchanged, but by varying X, we are able to



. . . . . (type i)

make a comparative study of a series of compounds, such as the phenyl halides (type ii).

C_6H_5F, C_6H_5Cl, C_6H_5Br, C_6H_5I . . . . . (type ii)

A practical example of the type (i) series occurs when X is a bromine atom. Pullman, Rumpf, and Kieffer (*J. Chim. phys.*, 1948, **45**, 150) have indicated that the charge density on the bromine atom is a predominant factor in determining the rate of isotopic bromine-exchange reactions. A second example is provided by α- and β-chloronaphthalene, where Ketelaar and van Oosterhout's detailed numerical calculations (*Rev. Trav. chim.*, 1946, **65**, 449) show a larger resonance energy in the former than in the latter. This conclusion could have been immediately predicted on the basis of equation (2) below. Another example is when X is OH, for the charge shift should measure to some extent the acidity of the corresponding phenols. Similarly, when X is NH_2 we expect to be able to discuss such quantities as the difference in basicity of α- and β-naphthylamine. [However, some caution is needed in this latter case because dipole-moment evidence suggests strongly that the three bonds at the nitrogen atom are not coplanar, so that the two conjugating electrons from the nitrogen are not strictly π-electrons, but have approximately tetrahedral hybrid forms which do bear a slight resemblance to π-orbitals. Our later general analysis will probably still apply, though perhaps with a reduced resonance integral β_{ar}. A somewhat similar caution is needed when X is a sulphide radical, such as SH, for as Longuet-Higgins (*Trans. Faraday Soc.*, 1949, **45**, 173) and Moffitt (*Proc. Roy. Soc.*, 1950, *A*, **200**, 409) have shown, *d*-electrons may play an important rôle in the type of bond formed.] As regards molecules of type (ii) a satisfactory analysis of the charge shifts is much to be desired, both qualitatively and quantitatively. For example, in qualitative discussions by organic

chemists, such as in the consideration of mesomeric dipole moments, one often finds such statements as: " since fluorine is more electronegative than chlorine, chlorine more electronegative than bromine, and bromine than iodine, the tendency of these atoms to send their two π-electrons into the benzene ring increases from fluorine to iodine." And in quantitative spectral studies variations in the parameter α which (see later) measures the electronegativity of X are often taken to be a sufficiently comprehensive factor as to be able to describe the frequency shifts that occur on substitution. It is true that Matsen (*J. Amer. Chem. Soc.*, 1950, **72**, 5243), when attempting such a discussion, found that in certain instances (including the halogenobenzenes) he was unable to absorb all differences in resonance integrals and all inductive effects in this one term; and he was obliged to introduce a second parameter, k' in our equation (2), to allow for this. The present analysis shows why this is necessary and in particular it underlines the significance of variations in the resonance integral, β_{ax}, which may be even more important than variations in α. This point does not appear to have been sufficiently stressed hitherto, although it could have been concluded from a number of numerical calculations made at various times by various authors.

Some analysis of the general problem of molecules AX has already been given by the present writers (*Trans. Faraday Soc.*, 1951, **47**, 681), who obtained a formula [formula (2), below] for the delocalisation energy due to the extra conjugation. This formula was closely similar to, though not identical with, the hydrocarbon formula (1).

$$-R_{ab} = k' + 0{\cdot}67(\pi_{a,a}/\alpha)^{\frac{1}{2}}\beta_{ab}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

[$\pi_{a,a}$ and β_{ab} have the same meaning as in (1). α is the coulomb term of the hetero-atom X, and k' is a constant measuring the inductive effect of X on the coulomb term of carbon atom a.]

We shall return to this formula later. From our present point of view it suffers from the drawback that it is not valid for small values of α, and it is obtained by a type of analysis which is not easily extended to deal with the bond order, p_{ax}, and charge distribution, q_x. We shall therefore develop alternative formulæ of a similar kind, applicable to all three measures of the conjugation. Afterwards we shall discuss their significance.

Let us return to Fig. 2, in which X is a group such as a halogen, and A is an alternant hydrocarbon. Then, in the notation used by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **191**, 39), let $\Delta(\varepsilon)$ be the secular determinant of the combined system, and $A(\varepsilon)$ that of the hydrocarbon residue A. Further, let α denote the coulomb term of the atom X, all energies being measured relative to a π-electron of a carbon atom. For the moment we shall not introduce any inductive effect, so that the coulomb term of atom a is supposed to be the same in the system AX as it was originally in the unsubstituted hydrocarbon AH. Later on, however, we shall use the symbol k' [Coulson and de Heer, equation (3)] to denote the change in coulomb term at atom a when the presence of X induces an increase in effective electronegativity of this atom. We may expect k' to be much smaller numerically than α, and to range from molecule to molecule in a closely similar way. The notation $\Delta_{r,s}$ or $A_{r,s}$ will mean that in each case the r'th row and s'th column have been struck out of the determinants. We have introduced these definitions because they allow us to use certain formulæ for q_x, the total mobile charge on X; for R_{ax}, the conjugation energy; and for p_{ax}, the mobile bond order of the bond a–X, which were given by Coulson and Longuet-Higgins (*loc. cit.*). The first of these formulæ is:

$$q_x = 1 - \frac{1}{\pi i}\int_{-\infty i}^{\infty i} \frac{\Delta_{x,x}}{\Delta} \cdot \mathrm{d}z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

However, $\Delta_{x,x}$ is simply A, and, with the usual neglect of all overlap integrals, we may write $\Delta(z) = (\alpha - z) \cdot A(z) - \beta_{ax}^2 \cdot A_{a,a}(z)$, so that

$$q_x = 1 - \frac{1}{\pi i}\int \frac{A(z)}{(\alpha - z) \cdot A(z) - \beta_{ax}^2 \cdot A_{a,a}(z)} \cdot \mathrm{d}z \quad . \quad . \quad . \quad (4)$$

No further general progress is possible with this integral, but if we may expand the integrand in powers of β_{ax} (effectively β_{ax}/β, where β is the normal carbon–carbon resonance integral), we have an approximation which has frequently been used, and (see later) shown to be remarkably good. Accepting this simplification, which should certainly serve to indicate the relative importance of quantities such as α and β_{ax}, we find that

$$q_x = 1 - \frac{1}{\pi i}\int_{-\infty i}^{\infty i}\left[\frac{1}{\alpha - z} + \frac{\beta_{ax}^2 \cdot A_{a,a}(z)}{(\alpha - z)^2 \cdot A(z)} + \ldots.\right]\mathrm{d}z$$

The first integral gives $-\pi i$, and the second can be simplified since $A(z)$ and $A_{a,a}(z)$ are polynomials of even and odd degree, respectively, in z. We have, finally,

$$q_x = 2 + \frac{2\alpha\beta_{ax}^2}{\pi}\int_{\infty}^{\infty}\frac{-iy \cdot A_{a,a}(iy)}{(\alpha^2 + y^2)^2 \cdot A(iy)} \cdot \mathrm{d}y + \ldots. \quad (5)$$

Since α is negative [otherwise the basic integral (3) is not valid] this means that a charge equal approximately to

$$\frac{-2\alpha\beta_{ax}^2}{\pi}\int_{-\infty}^{\infty}\frac{-iy \cdot A_{a,a}(iy)}{(\alpha^2 + y^2)^2 \cdot A(iy)} \cdot \mathrm{d}y \quad (6)$$

has migrated from X into the aromatic residue A.

If we now make the same calculation again, though including the inductive term k', we find, to the first degree in k', that the result in equation (6) still holds good. The earlier work by Coulson and de Heer, as expressed in equation (2), suggests that in this type of approximation we may regard the first-order term in k' as being on the same footing as the term in β_{ax}^2. This means that for our present purposes, we may retain equation (6) in its original form, whether or not the inductive effect is included.

A similar analysis may be applied to the asymptotic expansion of the conjugation energy, R. Equation (9) of Coulson and de Heer's paper shows us that this may be put in the form :

$$-R = k' + \frac{\beta_{ax}^2}{\pi}\int_{-\infty}^{\infty}\frac{A_{a,a}(iy)}{(\alpha - iy) \cdot A(iy)} \cdot \mathrm{d}y$$

This transforms to :

$$-R = k' + \frac{\beta_{ax}^2}{\pi}\int_{-\infty}^{\infty}\frac{iy \cdot A_{a,a}(iy)}{(\alpha^2 + y^2) \cdot A(iy)} \cdot \mathrm{d}y \quad (7)$$

In an exactly analogous way, we can adapt Coulson and Longuet-Higgins's equation (11) (*loc. cit.*, 1948) to give equation (8), which is valid whether or not the inductive effect is included. The result is :

$$p_{ax} = -\frac{\beta_{ax}}{\pi}\int_{-\infty}^{\infty}\frac{-iy \cdot A_{a,a}(iy)}{(\alpha^2 + y^2) \cdot A(iy)} \cdot \mathrm{d}y + \ldots. \quad (8)$$

in which the next two terms on the right-hand side are multiples of β_{ax}^3 and $k'\beta_{ax}$.

Equations (6), (7), and (8) give us a measure of the conjugation, as reflected in charge flow, energy, and bond order, respectively. All three results are obtained by considering only the initial terms of a power-series expansion. However the second equation (for the energy) has been carefully discussed by Coulson and de Heer in an equivalent form to that which we have used, and they showed that for all reasonable values of the parameters it was valid to within a few per cent. We may therefore presume that the same is true for the other equations, (6) and (8). We shall therefore discuss all three equations together in terms of the variations which they predict with k', β_{ax}, and α.

In the first place we notice that the inductive effect, as measured by k', is only significant for the conjugation energy. It appears to exert only a second- or third-order effect on charge migration and bond order.

Next let us consider the limiting forms taken by equations (6)—(8) when the attached atom X is strongly electronegative, so that $|\alpha|$ is large. We see that :

the conjugation energy varies as β_{ax}^2/α^2 (excluding the term k'), the charge migration varies as β_{ax}^2/α^3, and the bond order varies as

$$\beta_{ax}/\alpha^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

These three results show that in every case the conjugation across the bond depends on the resonance integral, β_{ax}, as much as on the coulomb term (or electronegativity), α. This means that any discussions which deal only with the coulomb term must necessarily be inadequate. The physical explanation of this is that whereas α measures the attraction for electrons of the atom X, β_{ax} measures the attraction of the bond a–X. In order that there may be effective conjugation, it is certainly necessary that β_{ax} should not be too small.

If we pass to the other extreme and consider the case where $|\alpha|$ is small, so that X is not very electronegative compared with carbon, instead of equation (9) we have that: the conjugation energy varies as β_{ax}^2 (excluding the term k'), the charge migration varies as $\beta_{ax}^2/(\beta_{ax}^2 + \text{constant})$, and the bond order varies as

$$\beta_{ax} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The only difficult formula here is that for the charge migration. It is not possible to let $\alpha \longrightarrow 0$ in equation (5) on account of convergence difficulties. Consequently we must return to equation (4), from which it may be shown that:

$$q_x = 1 + \frac{A(0)}{A(0) + \beta_{ax}^2 \cdot A_{a,a}'(0)} \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

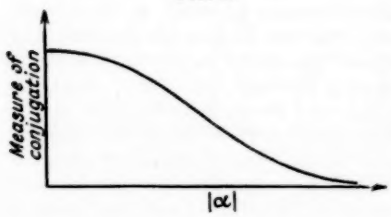
when α is identically zero. This implies that the charge migration $(2 - q_x)$ away from the atom X is:

$$\beta_{ax}^2 \cdot A_{a,a}'(0)/[A(0) + \beta_{ax}^2 \cdot A_{a,a}'(0)] \quad . \quad . \quad . \quad . \quad . \quad (12)$$

This is the result quoted in equation (10). In any actual example the numerical value of expression (12) may often be found most easily by a simple extension of the type of argument introduced by Longuet-Higgins (*J. Chem. Phys.*, 1950, **18**, 275).

For values of α intermediate between the two extreme values in (9) and (10) it is not hard to trace the variation of R (excluding k'), q_x, and p_{ax}. All three quantities are described by curves similar in general shape to that shown in Fig. 3. The details of these curves must obviously depend on the resonance integral, β_{ax}, and the choice of hydrocarbon, AH. In every case, however, β_{ax} plays at least as important a rôle as α, and often it is more important.

FIG. 3.



The results expressed by (9) and (10) show us clearly how it comes about that one single parameter such as α (Matsen's δ, *loc. cit.*) is unable to account for all those conjugation phenomena. For example it is quite evident from the form of the equations that variations in α cannot possibly absorb variations in β, though this may be approximately possible if we restrict our attention to just one of the three measures of conjugation. Any agreements with observation which are obtained in such a one-parameter way must be regarded as largely empirical.

The expressions (9) and (10) can also be used to throw light on certain resonance dipole moments. In a compound such as PhX it is reasonable to suppose that the difference $\alpha_x - \alpha_c$ (our previous α) is roughly proportional to the difference in electronegativities $|x_x - x_c|$, or at very least varies in the same general manner. Now Wheland ("Theory of Resonance," John Wiley, 1944, p. 132) has collected a table of experimental dipole moments. In particular he has compared the differences, $\mu_{RX} - \mu_{PhX}$, where X is a halogen and R is an alkyl group of approximately the same size as Ph (this is to give as

nearly equal polarisabilities as possible in R and Ph, and to make the back-polarisations due to the residual charges on the halogens as nearly the same as we can, in the two molecules). It appears from Wheland's table that the difference, $\mu_{RX} - \mu_{PhX}$, has a value 0·58 D when X is iodine, an atom for which Pauling gives a zero electronegativity difference. Thus the resonance moment here cannot arise from the coulomb term, α_I. According to our present description the charge migration must be due to the smaller $|\beta|$ for the π electrons in C–I rather than for those in C=C. The direction, of course, is just what would have been expected on our theory. In this way we confirm the importance of β in the determinations of resonance effects across a " single " bond.

In addition to this we may compare resonance moments for the cases where X is either Cl, Br, or I; Wheland gives the corresponding numerical values as 0·42, 0·49, and 0·58 D. Now the positive ends of these dipoles are assuredly on, or very near to, the halogen, and the negative ends must be somewhere just inside the benzene ring. If we recognise that the C–X distances are 1·77, 1·91, and 2·10 Å, respectively, we see that the actual charge migrations responsible for these resonance moments must be very nearly equal in all three molecules. This equality of charge $(2 - q_x)$ must be compared with the corresponding electronegativity differences, which are far from being equal, and are actually 0·5, 0·3, and 0. It is true that the resonance moments which we have quoted must not be treated too seriously. For the choice of alkyl radical R is not unique, and, as Mulliken and Coulson have shown, the resolution of the total molecular dipole moment into σ- and π-contributions is complicated by homopolar dipoles and hybridisation dipoles. Nor is it completely accurate to infer the charge migrations simply by dividing the resonance moments by some effective separation of the positive and negative charges. But when all this is taken into account, it is still fair to conclude that the resonance moments are evidently not governed solely, or even chiefly, by electronegativity differences. When we recall that the bond energies of C–Cl, C–Br, and C–I, as given by Pauling, are respectively 67, 54, and 46 kcal./mole, so that the β_{Cx} values will presumably follow a similar type of relationship, it is clear that there is strong experimental support for a charge-migration formula such as is implied in the expressions (9) and (10). A more precise numerical verification will only be possible when more is known than at present about the α's and β's between carbon and various hetero-atoms.

Reference must be made to the neglect of all overlap integrals. Now the works of Chirgwin and Coulson, of de Heer, and of Löwdin (*J. Chem. Phys.*, 1950, **18**, 365) all show that for alternant hydrocarbons the inclusion of these integrals makes absolutely no difference, and for certain mono-substituted ones, the difference is small, at least when equation (1) is applied. It seems fairly certain that this will also be true for the results of expressions (9) and (10). The most intuitive reason for this belief is that our formulæ relate essentially to the " initial stage " of a conjugation process. In such a stage the original alternant hydrocarbon is only slightly distorted, and we should therefore expect that conclusions which were valid for the alternant hydrocarbon itself would not thereby be gravely invalidated. This conclusion finds support from an " initial stage " calculation employing the technique suggested by Löwdin. We shall not reproduce the analysis, as it is of no great interest. But it can be shown, for example, that the charge migration is still given by an expression formally almost equivalent to equation (6), though with α replaced by $\alpha - \beta_{ax}S_{ax}$ and with β_{ax} replaced by $\beta_{ax} - \alpha S_{ax}$, where S_{ax} is the overlap integral, $\int \phi_a \phi_x d\tau$. All this justifies our belief that, except for very electronegative substituents, the qualitative conclusions of expressions (9) and (10) will not be seriously affected by the inclusion of overlap.

Conclusions.—The simple conclusions to be drawn from this study are: (1) conjugation across a single bond may be measured in terms of delocalisation energy, charge migration, or bond order: the three relevant formulæ show a close similarity to each other, and in particular the delocalisation-energy and bond-order values are almost proportional; (2) in every case the resonance integral is as important as the coulomb term in determining the extent of the additional conjugation; (3) increasing the electronegativity of a substituent X without any change in the resonance integral reduces the degree to which it can conjugate with the initial hydrocarbon; and (4) a proper quantitative understanding

of this type of conjugation is quite impossible until more information is available of the way in which the resonance integral between dissimilar atoms depends on the nature and environment of the atoms concerned.

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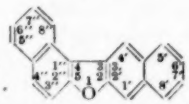
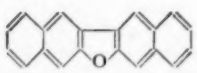
93. *Identification of* "iso*Dinaphthylene Oxide*" *as Dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan; Some Functional Derivatives of the Latter.*

By NG. PH. BUU-HOÏ.

"*iso*Dinaphthylene oxide" resulting from the calcium oxide-catalysed oxidodehydration of β-naphthol (Clemo and Spence, *J.*, 1928, 2811) is found to be identical with dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan, prepared by zinc dust distillation of the corresponding 5 : 8-quinone. Several functional derivatives of the latter have been prepared from 2 : 3-dichloro-1 : 4-naphthaquinone; this quinone proved to be a sensitive reagent for the characterisation of β-naphthols having a free adjacent α-position.

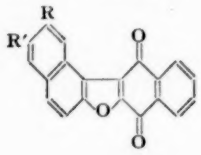
THE six isomeric dinaphthofurans have come under consideration in this Institute because of their molecular resemblance to the corresponding dibenzofluorenes, some of which are known inhibitors of the growth of grafted tumours (Badger *et al.*, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255; Haddow, quoted by Cook and Stephenson, *J.*, 1949, 842), and of the carcinogenic action of methylcholanthrene and other similar hydrocarbons (Lacassagne, Buu-Hoï, and Cagniant, *Compt. rend. Soc. Biol.*, 1944, **138**, 16; Lacassagne, Buu-Hoï, and Rudali, *Brit. J. Exp. Path.*, 1945, **26**, 5). The most accessible dinaphthofuran is "*iso*dinaphthylene oxide," prepared by Clemo and Spence (*J.*, 1928, 2811) by prolonged heating above 280° of β-naphthol in the presence of alkali-earth oxides. The fact that this substance underwent chromic oxidation to a *p*-monoquinone, as well as the interpretation of spectroscopic data (Clemo, Cockburn, and Spence, *J.*, 1931, 1265), led those authors to give preference to formula (I) for its constitution, rather than the alternative formula (II):

(I)  (II) 

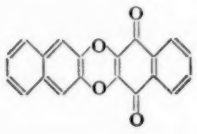
There has not, however, as yet been any rigid proof for this constitution; confirmation of Clemo and Spence's assumption is now offered by the synthesis of dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan (I) and its identification with "*iso*dinaphthylene oxide." Dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan-1′ : 4′-quinone (III; R = R′ = H) was prepared by condensation of β-naphthol with 2 : 3-dichloro-1 : 4-naphthaquinone in pyridine solution (Eistert, *Ber.*, 1947, **80**, 52), and found identical with the quinone prepared from "*iso*-dinaphthylene oxide" by oxidation. That β-naphthol links with 2 : 3-dichloro-1 : 4-naphthaquinone at the 1- and not the 3-position is proved by the inability of 1-substituted 2-naphthols (for example, 1-methyl-2-naphthol) to give such furan derivatives. Conversely, zinc dust distillation of a sample of the quinone prepared by Eistert's method yielded a compound $C_{20}H_{12}O$ which was found identical with "*iso*dinaphthylene oxide."

The formation of furan derivatives from 2 : 3-dichloro-1 : 4-naphthaquinone is characteristic of homologues of β-naphthol having a free adjacent α-position, as shown by the ready preparation of 6″-methyl- (III; R = H, R′ = Me), 6″-*n*-propyl- (III; R = H, R′ = Pr^n), and 6″-*tert.*-butyl-dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan-1′ : 4′-quinone (III; R = H, R′ = Bu^t) from 6-methyl-, 6-*n*-propyl-, and 6-*tert.*-butyl-2-naphthol respectively. From 6-bromo-2-naphthol, the 6″-bromo-quinone (III; R = H, R′ = Br) could also be

prepared without loss of bromine, whereas with 2-hydroxy-3-naphthoic acid the non-substituted quinone (III; R = R′ = H) formed by partial decarboxylation could be isolated. In the case of heteronuclear amino-derivatives of β-naphthol, routine furan cyclisation was accompanied by the reaction of another molecule of 2 : 3-dichloro-1 : 4-



(III)



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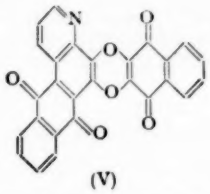
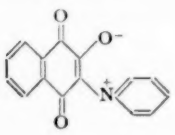


(V)

naphthaquinone upon the amino-group (cf. Plagemann, *Ber.*, 1882, **15**, 484; Brass, *Ber.*, 1912, **45**, 2531; Fries and Ochwat, *Ber.*, 1923, **56**, 1317; Buu-Hoï, *Bull. Soc. chim.*, 1944, **11**, 578); thus, from 7-amino-2-naphthol, 7″-(2-chloro-1 : 4-naphthaquinon-3-yl)dinaphtho-(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan-1′ : 4′-quinone was obtained.

It was interesting to investigate whether the three dihydroxynaphthalenes bearing both hydroxyl groups in the β-position would give double furan cyclisation with two molecules of 2 : 3-dichloro-1 : 4-naphthaquinone : in none of the three cases was this found possible. 2 : 3-Dihydroxynaphthalene yielded dinaphtho(2′ : 3′-2 : 3)(2″ : 3″-5 : 6)dioxin-1 : 4-quinone (IV), a reaction similiar to that observed by Ullmann and Ettisch (*Ber.*, 1921, **54**, 259) with catechol; 2 : 6- and 2 : 7-dihydroxynaphthalene yielded 6″-hydroxy- (III; R = H, R′ = OH) and 7″-hydroxy-dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)furan-1′ : 4′-quinone (III; R = OH, R′ = H), whether one or two molecules of 2 : 3-dichloro-1 : 4-naphthaquinone were used. The methyl ethers of the last two substances could be prepared either by treatment with methyl sulphate of their deep blue solutions in aqueous sodium hydroxide, or more directly by condensation of 6-methoxy- and 7-methoxy-2-naphthol with 2 : 3-dichloro-1 : 4-naphthaquinone.

Whereas 2 : 3-dichloro-1 : 4-naphthaquinone is known to react with pyridine to give the betaine (VI) (Ullmann and Ettisch, *loc. cit.*), normal condensations were observed on the one hand with alizarin blue (3 : 4-dihydroxy-4′-aza-1 : 2-benzanthra-9 : 10-quinone) to form the benzodioxin compound (V), and on the other hand, with 6 : 2′-quinolyl-2-naphthol



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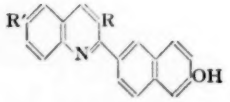
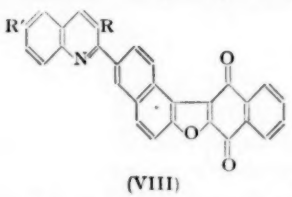


(VII)



(VIII)

and several of its derivatives (VII) to give the expected furan compounds (VIII). The affinity of the chlorine atoms in 2 : 3-dichloro-1 : 4-naphthaquinone towards heterocyclic nitrogen is thus inferior to that towards phenolic groups.

A characteristic property of all the furan-quinones mentioned in this work is the deep blue colour of their solutions in pure sulphuric acid. This colour test (which is also given by brasanquinone and its derivatives) might be of interest for the detection of a β-naphthol group having the adjacent α-position free, a problem frequently encountered in the study of certain natural products.

Experimental

Dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone.*—(a) *By Eistert's method.* Eistert's procedure (*loc. cit.*) was modified in the following way: A mixture of 2 : 3-dichloro-1 : 4-naphthaquinone (2·3 g.), β-naphthol (1·5 g.), and anhydrous pyridine (10 c.c.) was cautiously heated to the b. p., whereon a violent reaction set in, the colour of the solution changing to

deep brown-red. The mixture was refluxed for a further hour; after cooling, the orange crystalline cake was treated with methanol, collected, washed with water, and recrystallised from acetic acid. The shiny orange-yellow needles obtained (2·8 g.) had m. p. 271—272°, and gave an intense greenish-blue colour with sulphuric acid.

(b) *From* "iso*dinaphthylene oxide*." Oxidation of this compound was much shortened when potassium dichromate and dilute sulphuric acid (Clemo and Spence, *loc. cit.*) were replaced by chromic acid in acetic acid medium. The m. p. of the quinone obtained (271—272°) was not depressed on admixture with the sample mentioned above; the colour with sulphuric acid was also the same.

Dinaphtho(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan* (I).—An intimate mixture of one part of the quinone prepared by Eistert's method with ten parts of dry zinc dust was heated in a vacuum, and the yellow distillate crystallised several times from acetic acid; the pale yellow needles obtained had m. p. 159°, alone or mixed with "*iso*dinaphthylene oxide." The yellow colour of this compound is probably due to traces of an impurity (possibly perylene), as a sample purified by chromatography was almost colourless. The molecular compound with 1 : 3 : 5-trinitrobenzene formed from benzene silky deep orange prisms, m. p. 175°.

6″-*Methyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*.—6-Methyl-2-naphthol was prepared from β-methylnaphthalene according to Dziewoński, Schoenówna, and Waldmann (*Ber.*, 1925, **58**, 1213); a solution of this compound (1·8 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (2·3 g.) in pyridine (10 c.c.) was treated as above; the *quinone* (3 g.) obtained crystallised on cooling, and formed from xylene long silky orange-yellow needles, m. p. 270° (Found : C, 80·6; H, 3·8. $C_{21}H_{12}O_3$ requires C, 80·8; H, 3·8%).

6-n-*Propyl*-2-*naphthol*.—This *compound* (2 g.) was prepared by demethylation with pyridine hydrochloride (10 g.) of the product from the Clemmensen reduction of 6-propionyl-2-methoxynaphthalene (6 g.); it formed from ligroin silky colourless needles, m. p. 81° (Found : C, 83·6; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). 6″-n-*Propyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* was readily soluble in xylene, and formed fine silky orange needles, m. p. 212° (Found : C, 81·0; H, 4·6. $C_{23}H_{16}O_3$ requires C, 81·2; H, 4·7%).

6″-tert.-*Butyldinaphtho*(2′ : 3′ : 2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*.—This *quinone* formed from toluene shiny golden-yellow leaflets, m. p. 239—240° (Found : C, 80·9; H, 5·0. $C_{24}H_{18}O_3$ requires C, 81·3; H, 5·1%); 6-*tert.*-butyl-2-naphthol was prepared according to Buu-Hoï *et al.* (*J. Org. Chem.*, 1950, **15**, 1060).

6″-*Bromodinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* formed from pyridine shiny light orange-yellow, sublimable needles, m. p. 308° (Found : C, 63·3; H, 2·2. $C_{20}H_9O_3Br$ requires C, 63·7; H, 2·4%); a compound with similar properties was obtained by chromic oxidation of " dibromo*iso*dinaphthylene oxide " (Clemo and Spence, *loc. cit.*), but with a somewhat lower m. p. (300—301°).

7″-(2-*Chloro*-1 : 4-*naphthoquinon*-3-*yl*)*dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*.—A solution of 7-amino-2-naphthol (2 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (4 g.) in pyridine (15 c.c.) was refluxed for 6 hours. After cooling, the precipitate was collected, washed with ethanol, and recrystallised from pyridine or nitrobenzene, to give the *quinone* as fine brown prisms, m. p. > 340°, giving with sulphuric acid a deep blue-violet colour (Found : C, 71·2; H, 3·4. $C_{30}H_{14}O_5NCl$ requires C, 71·4; H, 2·8%).

7″-*Hydroxydinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*.—A solution of 2 : 7-dihydroxynaphthalene (2 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (2·3 or 4·6 g.) in pyridine (15 c.c.) was refluxed for 18 hours; the orange precipitate obtained on cooling formed from pyridine silky red, sublimable needles (2 g.), m. p. > 340°, giving with sulphuric acid a Prussian-blue colour (Found : C, 76·0; H, 3·3. $C_{20}H_{10}O_4$ requires C, 76·4; H, 3·2%). The *methyl ether*, prepared by direct methylation or from 7-methoxy-2-naphthol, formed from xylene fine orange needles, m. p. 255—256° (Found : C, 76·5; H, 3·5. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

6″-*Hydroxydinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* separated from acetic acid as either red, sharp prisms, or silky orange needles, m. p. 317—318° (decomp.) (Found : C, 76·2; H, 3·2%). The *methyl ether* formed from xylene orange-yellow prisms, m. p. 281—282° (Found : C, 76·5; H, 3·6%).

Dinaphtho(2′ : 3′-2 : 3)(2″ : 3″-5 : 6)*dioxin*-1 : 4-*quinone* formed from pyridine shiny brown-red, sublimable needles, m. p. > 340°, giving with sulphuric acid a violet colour, changing to brown (Found : C, 76·1; H, 3·1. $C_{20}H_{10}O_4$ requires C, 76·4; H, 3·2%). The *diquinone* (V), prepared from alizarin-blue (4 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (2 g.) in pyridine (15 c.c.), formed dark blue microcrystals, m. p. > 340° (Found : C, 72·4; H, 2·3. $C_{27}H_{11}O_6N$ requires C, 72·8; H, 2·5%).

6″-(2-*Quinolyl*)*dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (VIII; R = R′ = H).—6-2′-Quinolyl-2-naphthol was prepared by demethylation of the corresponding methyl ether (Buu-Hoï, *Rec. Trav. chim.*, 1949, **68**, 759) with pyridine hydrochloride, and basification with aqueous ammonia of the orange-yellow, water-insoluble hydrochloride. The *quinone* formed with 2 : 3-dichloro-1 : 4-naphthaquinone yielded, from pyridine, silky orange needles, m. p. 302—303° (Found: C, 81·8; H, 3·6. $C_{29}H_{15}O_3N$ requires C, 81·9; H, 3·5%).

6″-(6-*Bromo*-2-*quinolyl*)*dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (VIII; R = H, R′ = Br).—6-(6-Bromo-2-quinolyl)-2-naphthol was prepared as above; the *quinone* formed from pyridine shiny orange prisms, m. p. 336° (Found: N, 2·7. $C_{29}H_{14}O_3NBr$ requires N, 2·8%).

6″-(3-*Methyl*-2-*quinolyl*)*dinaphtho*(2′ : 3′-2 : 3)(11′ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (VIII; R = Me, R′ = H), prepared from 6-(3-methyl-2-quinolyl)-2-naphthol, formed from pyridine silky orange needles, m. p. 284—285° (decomp.) (Found: N, 3·1. $C_{30}H_{17}O_3N$ requires N, 3·2%).

6″-(6-*Bromo*-3-*methyl*-2-*quinolyl*)*dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (VIII; R = Me, R′ = Br).—6-(6-*Bromo*-3-*methyl*-2-*quinolyl*)-2-*naphthol* (VII; R = Me, R′ = Br) formed from ethanol shiny colourless needles, m. p. 260—261° (Found: C, 65·6; H, 4·0. $C_{20}H_{14}ONBr$ requires C, 65·9; H, 3·8%); the *quinone* crystallised from pyridine in orange prisms, m. p. 279° (decomp.) (Found: C, 69·1; H, 3·0. $C_{30}H_{16}O_3NBr$ requires C, 69·5; H, 3·1%).

6″-(6-*Bromo*-3-*phenyl*-6-*quinolyl*)*dinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone* (VIII; R = Ph, R′ = Br), prepared from 6-(6-bromo-3-phenyl-2-quinolyl)-2-naphthol, formed from pyridine as fine orange prisms, m. p. 275—276° (decomp.) (Found: C, 72·2; H, 3·2. $C_{35}H_{18}O_3NBr$ requires C, 72·4; H, 3·1%).

In carcinogenesis tests, performed in this Institute, "*iso*dinaphthylene oxide" proved to be inactive, in confirmation of earlier findings by Barry *et al.* (*Proc. Roy. Soc.*, 1935, *B*, **117**, 346).

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94. *Absorption of Electrolyte by Alginate Gels without and with Cation Exchange.*

By I. L. MONGAR and ALBERT WASSERMANN.

Various stoicheiometric relationships characterising the interaction of fully swollen fibrous alginates with simple electrolytes are established. It is shown that these gels are cation-exchange materials, and equilibrium concentration coefficients pertaining to one particular exchange reaction are determined.

IT is known that the main valency chains of macromolecules can be induced to change their shape as the result of divers chemical reactions, and that alterations of molecular configuration can give rise to considerable changes of the physical properties of the materials containing the high polymers. In this series of papers experiments are reported which show that a curling up of stretched, chain-like, giant molecules, and the accompanying macroscopic effects, can be brought about by stoicheiometrically well-defined simple metatheses. The high polymers used for this work are alginates (polymeric D-mannuronic acid derivatives), and the reactions responsible for alterations of molecular shape are cation-exchange processes. This paper deals with the preparation of fully swollen, cylindrical alginic acid and alginate gels and with the absorption of simple electrolytes by these materials. The results provide the analytical background for effects discussed in a later paper.

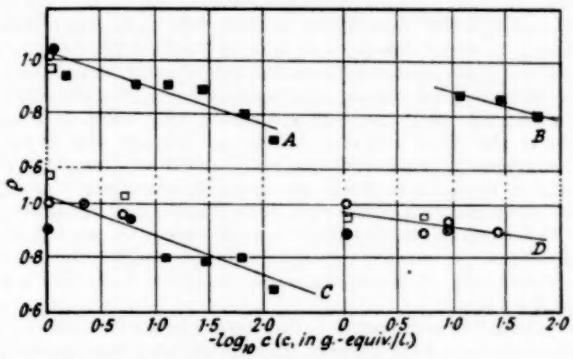
EXPERIMENTAL

A 5% solution of sodium alginate (dry weight basis) of number average molecular weight 10^5 * was thoroughly freed from dust and air bubbles and extruded in 1N-hydrochloric acid. [The molecular weights of sodium alginate quoted in this series of papers were estimated with the help of equation (2), *J.*, 1952, 497.] A fibrous gel was thus precipitated which, before being fully coagulated, was immediately extended by hand to 5—10 times its initial length and

* The intrinsic viscosity of this alginate, dissolved in 0·1N-sodium chloride, is 870 ± 40 cm.³/g., at 20°.

wound on rotating glass cylinders. In order to obtain fibres of sufficiently uniform diameter some practice is required, and the help of a collaborator who controls the speed of rotation of the supports. Similar methods of making alginate fibres have been described (cf. Speakman and Chamberlain, *J. Soc. Dyers Col.*, 1944, **60**, 264; Astbury, *Nature*, 1945, **155**, 667). The fibres were washed, placed in frequently renewed 0·1N-calcium acetate, until quantitative replacement of non-permeant sodium by calcium ions had taken place, washed again until free from permeant electrolyte,† and stored under water at 5°. Alginic acid and the various alginates were made shortly before use, by treating the fully-swollen calcium alginate gel with aqueous solutions of hydrochloric acid, the acetates or chlorides of magnesium, barium, sodium, or copper, silver nitrate, or aluminium sulphate. The treatment with the acid or the metal-salt solutions was frequently repeated until analytical tests showed that quantitative cation exchange had occurred. The gels were finally freed from permeant electrolytes by washing with water or with 25% ethyl alcohol. Before analysis, the surface of the fully-swollen gels was thoroughly

Absorption of simple electrolytes by fully swollen alginate gels under conditions not conducive for cation exchange.



Ordinates: Distribution ratio ρ as defined by equation (1).
Abscissæ: Negative logarithm of equilibrium concentration, c, of electrolyte in aqueous phase (c in g.-equiv./l.).

Symbol *	Temp.	Surface/volume ratio of fibres (cm.$^{-1}$)	Method of measurement	Symbol *	Temp.	Surface/volume ratio of fibres (cm.$^{-1}$)	Method of measurement
□	40—60°	100	I	⊗	20	35	I
○	15—20		I	■	20	250	II
●	5—7		I				

* The size of the symbols in the figure indicates the error of these measurements.
(*A*) Alginic acid + HCl; (*B*) Silver alginate + $AgNO_3$; (*C*) Calcium alginate + $CaCl_2$; (*D*) Calcium alginate + NaCl (see p. 496).

dried by means of filter-paper strips; the accuracy of this method, for fibres 100 cm. long and weighing about 1 g., was ±1%. The diameter of these fully-swollen fibres, of known specific gravity, could be calculated from weight determinations, done with a torsion balance, and length determinations, carried out as indicated later (*J.*, 1952, 500). These measurements required less than 30 sec., so the error due to evaporation of gel water was negligible. In some cases the fibre diameter was also estimated with a microscope containing a calibrated eye-piece scale.

Alginic acid was analysed by alkalimetric titration and by estimating the uronic acid carbon dioxide, an apparatus being used similar to that described by Whistler, Martin, and Harris (*Bur. Stand. J. Res.*, 1940, **24**, 13), the two methods giving results which agreed to within ±5%. The metal alginates were rinsed with 1N-hydrochloric or -nitric acid; the relevant cations were thereby dissolved and were estimated in the acid extract by standard methods, the remaining alginic acid gel being analysed as indicated above. Dry-weight was

† Here and below, the term " permeant electrolyte " refers to one which can be removed from the alginate gel by sufficiently long washing with water of pH 5. The counter ions, *e.g.*, calcium or sodium, which remain in the gel under such conditions, are termed " non-permeant."

found by drying at 80°/1 mm. Representative results of an analysis of calcium alginate were: Dry weight, 8·1 ± 0·2 g. per 100 g. of fully-swollen surface-dry fibre; Ca, 4·84 ± 0·09 × 10^{-3} g.-equiv./g. of dry gel; CO_2H, 4·65 ± 0·15 × 10^{-3} g.-equiv./g. of dry gel; Ca/CO_2H, 1·04 ± 0·06; equiv., 208 ± 8. The absence of sodium was established by digesting the calcium alginate with concentrated nitric acid and testing the residue in the usual way with magnesium uranyl acetate.

Absorption measurements of electrolytes, under conditions not conducive for cation exchange, were made as follows: *Method* I. The freely suspended alginate fibre was rinsed with water at a known temperature; at zero time the flow was discontinued and the fibre was rinsed with the solution of an electrolyte which had been kept at the same temperature. When equilibrium was established, the surface of the fibre was quickly dried, the weight was taken, and the permeant electrolyte was removed by rinsing with water, an analysis of this effluent enabling a computation to be made of the distribution ratio, ρ, where

$$\rho = \frac{\text{g.-equiv. of permeant electrolyte absorbed by 1 g. of fully swollen gel}}{\text{g.-equiv. of electrolyte in 1 g. of equilibrium solution}} \qquad (1)$$

Method II. In carrying out measurements according to this method, the surface of the fibres was freed from excess of liquid by centrifuging at about 500 r.p.m., the reaction vessel being an inverted centrifuge cup in which the gel was kept in position by means of a closely fitting perforated Perspex disc. The distance between the axis of rotation and the centrifuge cup was 12 cm. After about 10 mins.' centrifuging, the decrease of weight of the centrifuged gel was less than 0·1% per min. At this stage the fibre was rinsed with water until free from permeant electrolyte; analysis of the initial solution, of the centrifugate, and of the washings, and a determination of the weight of the centrifuged gel, enabled an estimation to be made of the ρ values. The results of the measurements are shown in the figure. In (*A*), (*C*), and (*D*), a number of variables (concentration of solution, temperature, and surface/volume ratio of the gel) were altered. This explains the relatively large deviations of some of the points from the straight lines, the significance of which is merely to indicate, roughly, the general trend of all the distribution ratios of each set. It is not suggested, of course, that there is a linear functional relation between ρ and log c.

The results of experiments pertaining to cation exchange are in Table 1. The runs marked with an asterisk were done in a static system, while in all other tests the conditions were as in method I, the rate of flow of the electrolyte solution varying between 1 and 10 $cm.^3$/min., and the number of g.-equiv. of electrolyte in the solution passed over the fibre being at least twice as large as the number of g.-equiv. of alginate. The replacement ratio in the last column of the table is defined by

$$\alpha = \frac{\text{g.-equiv. of cation removed from original fibre}}{\text{g.-equiv. of cation transferred from solution into gel and combined with alginate}} \qquad (2)$$

The reactions can be classified into four groups from the point of view of analytical procedure. Group 1 comprises Nos. 1, 2, 5—12, 14, 15, 19, 20, 22, 24, and 26—28; in these runs no detectable amount of alginate dissolved (this being checked by total alginate estimation before and after reaction); and it was possible to wash out the low-molecular products of the ion exchange. In run No. 15, for instance, the gel, after being treated with the sodium chloride solution, was washed with water or aqueous ethyl alcohol until it was free from permeant electrolytes. The washing, e_2, was mixed with the effluent, e_1, obtained during the treatment with the sodium chloride solution, the replacement ratio being deduced from calcium determinations in $e_1 + e_2$ and from sodium estimations in the washed gel. Group 2 comprises the reactions Nos. 13, 16—18, 21, and 25 in which some of the alginate formed during the cation exchange dissolved, while a sparingly soluble salt was formed which remained in the gel. In the interaction between calcium alginate and sodium carbonate solution, for instance, the initial operations were as in run No. 15; it was necessary, however, to acidify the joint solutions $e_1 + e_2$, thereby precipitating free alginic acid which was determined as follows. The gel was centrifuged, and the precipitate transferred to a glass filter and converted into copper alginate by treating it with 0·5N-copper acetate. After removal of the permeant electrolyte, the copper alginate was decomposed with N-hydrochloric acid, the alginic acid being estimated by titrating the dissolved cupric ions. The washed calcium sodium alginate gel, contaminated with the calcium carbonate formed during the ion exchange, was introduced into an apparatus suitable for the determination of carbonate carbon dioxide, this being determined after addition of 1N-hydrochloric acid. (For an alternative method of analysis, see Mongar and Wassermann, *Nature*, 1947, **159**, 746.)

The figures in the last two columns of No. 16 of Table 1 could be calculated by taking into account the results of four sets of analyses, namely, the determination of calcium in the solution $e_1 + e_2$, alginic acid, carbonate carbon dioxide, and sodium, the last determination being done in the acid extract of the washed calcium sodium alginate gel. Group 3 comprises reactions 4 and 23, in which a sparingly soluble salt of non-stoicheiometric composition is formed. In No. 23, for instance, the basic copper carbonate, precipitated in the gel, had to be determined by

TABLE 1. *Absorption of simple electrolytes by fully-swollen alginate gels under conditions conducive to cation exchange* (Temp. ~20°).

Ref. No.	Gel	Fibre diam. (mm.)	Soln.	Concn. (g.-equiv./l.)	Time of absorption (sec.)	Non-permeant cation replaced (%)	Replacement ratio (a)
1	Alginic acid	0·5	$Ca(OAc)_2$	1·0	100—200	100	1·0 ± 0·05
2		0·7	NaCl	1·0	30	16	1·0 ± 0·05
3		0·8	NaOH	1·0	100—200	100	1·0 ± 0·05
4	Aluminium alginate	0·4	Na_2CO_3	0·2	30	49	1·3 ± 0·2
5	Barium alginate	0·5	HCl	1·0	600—800	100	1·0 ± 0·05
6	Calcium alginate	0·4	$AgNO_3$	1·0	25	85	0·95 ± 0·05
7		0·5	$Al_2(SO_4)_3$	2·6	30	71	2·0 ± 0·3
8		0·5	$Ba(OH)_2$	1·0	100—200	100	1·0 ± 0·5
9		0·4	$Cu(OAc)_2$	0·6	30	84	1·0 ± 0·05
10		0·5	HCl	1·0	600—800	100	1·0 ± 0·05
11		0·4	KCl	4	30	52	1·1 ± 0·2
12		0·4	$Mg(OAc)_2$	2·0	25	28	0·9 ± 0·1
13		0·5	Na_4ATP ‡	0·9	30	40	0·8 ± 0·2
14		0·4	NaOAc	2·0	20	44	0·9 ± 0·1
15		0·4	NaCl	1·0	30	31	0·9 ± 0·1
16		0·5	Na_2CO_3	2·0	20	20	1·1 ± 0·1
17		0·4	$Na_2C_2O_4$	0·33	20	30	1·1 ± 0·1
18		0·5	NaF	0·25	10	52	$\leqslant 1$
19		0·5	$NaHCO_3$	1·0	30	12	1·0 ± 0·1
20		0·5	NaOH	1·0	30	10	1·9 ± 0·2
21		0·5	Na_3PO_4	1·0	30	66	1·1 ± 0·1
22		0·5	Na_2SO_4	2·0	30	47	0·8 ± 0·2
23	Copper alginate	0·4	Na_2CO_3	2·0	30	71	0·8 ± 0·2
24 *	Magnesium alginate	0·5	NaOAc	2·0	100—200	100	1·0 ± 0·1
25	Silver alginate	0·5	NaCl	0·1	15	52	1·0 ± 0·1
26 *	Sodium alginate	0·8	HCl	1·0	600—800	100	1·0 ± 0·05
27	Sodium calcium † alginate	0·5	$Ca(OAc)_2$	1·0	200—400	100	1·0 ± 0·1
28	Sodium copper † alginate	0·5	$Cu(OAc)_2$	1·0	200—400	100	1·0 ± 0·1

† These gels were prepared by treating calcium or copper alginate with 1N-sodium chloride until about 50% replacement had taken place; the gels so obtained were washed with 25% ethyl alcohol–water.

‡ This symbol is an abbreviation for the sodium salt of adenosine triphosphate.

estimating the carbon dioxide evolved on addition of 1N-hydrochloric acid and by analysing a washed precipitate obtained by mixing 0·4N-copper acetate with an excess of 2N-sodium carbonate. It was furthermore necessary to analyse the sodium in the acid extract of the washed copper sodium alginate. Group 4 is represented by the reaction between alginic acid and sodium hydroxide, the replacement value being obtained in this case from the results of alkalimetric titrations. A mixed calcium sodium alginate, on being fully recalcified with 0·1N-calcium acetate, does not release a detectable quantity of hydrogen ions.

The reversible metathesis, calcium alginate + sodium chloride $\rightleftarrows$ mixed calcium sodium alginate + calcium chloride, is of particular importance for some of the experiments described in the following papers. This ion exchange is schematically represented as follows:

$$Ca_g^{\cdot\cdot} + 2Na^{\cdot} \rightleftarrows 2Na_g^{\cdot} + Ca^{\cdot\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $Ca_g^{\cdot\cdot}$ and $Na_g^{\cdot}$ are symbols for the non-permeant ions combined with the alginate residue. An equilibrium coefficient, characterising (3), can be defined by the expression

$$K = [Ca_g^{\cdot\cdot}][Na_s^{\cdot}]^2/[Na_g^{\cdot}]^2[Ca_s^{\cdot\cdot}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

the subscripts indicating that the relevant concentrations refer respectively to the gel phase and to the aqueous solution.

The equilibrium coefficients were determined by two methods : (*a*) Surface-dry, fully-swollen calcium alginate fibres, of known weight, were placed in a known volume of a sodium chloride solution, the concentration of which had been determined. After equilibrium, the calcium chloride concentration in the supernatant liquid was estimated. (*b*) The supernatant liquid was almost

TABLE 2. *Concentration equilibrium coefficients*, K, *characterising the reaction between fully swollen calcium alginate gels and sodium chloride solution* (Temp. ~20°).

Method	No. of runs	Fully-swollen, surface-dry calcium alginate fibres (g.)	Diam. of fibre (mm.)	Vol. of soln. ($cm.^3$)	Equil. concn. of solution : NaCl	$CaCl_2$	K *
a & *b*	10	0·16—1·0	0·2—0·8	5—11	0·8—1·0	0·002—0·015	60 ± 10
b	2	1·0	0·3	4—10	0·7—0·8	0·01—0·016	48 ± 6
a	5	0·16—1·0	0·2—1·0	10—50	0·4—0·6	0·006—0·0017	30 ± 10
b	6	0·48—1·2	0·3—0·9	10—50	0·06—0·19	0·0016—0·0024	10 ± 3
b	2	1·0	0·31	50	0·02—0·05	0·0004—0·0009	10 ± 3

* These K values are dimensionless because the concentration units of the various factors occurring in equation (4) are identical.

completely removed by centrifuging; the remaining gel was extracted with hydrochloric acid, calcium estimations being done in the centrifugate and in the acid extract. The results of these measurements are in Table 2. Tests under comparable concentration and volume conditions, done at 6·5°, 24°, 49°, and 65°, showed that K decreases with increasing temperature.

DISCUSSION

There is no marked difference between the distribution ratios, ρ, relating to the interaction of alginic and hydrochloric acid and those relating to the electrolyte absorption by the alginates (see figure), although the ionisation of the free acid is strongly repressed at pH values below 2 (Saris and Schofield, *Proc. Roy. Soc.*, 1946, *A*, **185**, 431). In three of the systems characterised by the graphs in the figure the permeant and the non-permeant cations are identical, while in system (*D*) the absorption of sodium chloride by the gel is followed by an ion-exchange reaction. It has been found (Mongar and Wassermann, *Discuss. Faraday Soc.*, 1949, **7**, 118) that the attainment of a stationary sodium chloride concentration in the gel is faster than the replacement of the non-permeant calcium by sodium ions and, therefore, the distribution ratios relating to this particular system could also be estimated. The distribution ratios vary between 0·68 and 1·04, although the electrolyte concentration in the outside solution varies over 100-fold. In the whole range, the stationary concentration of the permeant electrolytes in the gel is not markedly smaller than the electrolyte concentration in the outside solution.

The figures in Table 1 show that fully-swollen alginate gels are cation-exchange materials. In those runs in which the replacement ratio, α, is unity, within the limits of the experimental errors, a membrane hydrolysis could hardly play a predominant rôle. This view is consistent with observations mentioned on p. 495 which pertain to the recalcification of a mixed sodium calcium alginate gel; for, if the replacement of calcium by sodium ions, leading to the mixed alginate, had been accompanied by an uptake of hydrogen ions, the latter species would probably be released during the final recalcification. No such effect, however, could be detected. Membrane hydrolysis could operate, on the other hand, in reactions in which the replacement ratio differs markedly from 1, *e.g.*, in run No. 7 of Table 1. Other effects, however, could also play a rôle.

Turning now to the equilibrium measurements, the results of which are in Table 2, it should be noted that concentrations, not activities, are used in (4), and, therefore, it is not surprising that K depends on the electrolyte concentration. Equation (4) can be written in the form

$$X^3 + WV[NaCl_s]^2X/4K - yWV[NaCl_s]^2/4K = 0 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where X is the number of g.-mol. of permeant calcium in the equilibrium solution, y is the number of g.-mol. of calcium in the original gel, W is the volume of the gel, and V is that of

the solution. The expression, in conjunction with the knowledge of K, can be utilised in order to adjust the experimental conditions prevailing during the conversion of calcium alginate in such a manner as to introduce a specified quantity of sodium ions into the gel.

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95. *The Intrinsic Viscosity of Sodium Alginate.*

By M. L. R. HARKNESS and ALBERT WASSERMANN.

The viscosity of sodium alginate in solutions of simple electrolytes, $Na^{+}_{y}X^{y-}$, has been determined in order to estimate the average distance, $2R_s$, between the ends of the alginate chains. In 0·1N-electrolyte solutions the R_s values are not markedly influenced by the nature of X, but in more concentrated solutions a significant anion effect obtains. It is shown, moreover, that in these solutions the alginate chains are not fully extended.

THE viscosity of alginate solutions has been measured by Rose (Ph.D. Thesis, London, 1937), Lunde *et al.* (*Kolloid Z.*, 1938, **83**, 208), Pauli and Stenbach (ibid., **84**, 291), Saverbone ("A Contribution to the Knowledge of Acid Poly-uronides," Upsala, 1945), Deuel and Weber (*Helv. Chim. Acta*, 1945, **28**, 1096), and Donnan and Rose (*Canadian J. Res.*, 1950, **28**, *B*, 105). These experiments show that in the presence of simple electrolytes the dependence upon concentration of the ratio

$$\frac{\text{Specific viscosity * of sodium alginate solution}}{\text{Concentration of sodium alginate}} = \frac{\eta_{sp.}}{c} \quad . \quad . \quad . \quad (1)$$

is of a nature which permits a fairly reliable estimation of the intrinsic viscosity $[\eta] = \lim_{c \to 0} (\eta_{sp.}/c)$. Rose (*loc. cit.*) determined the number average molecular weight, M_n, of several sodium alginate samples and his results show that the intrinsic viscosity, relative to 0·1N-sodium chloride solution, can be represented by

$$[\eta] = AM^B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $A = 10^{-2\cdot5\pm1}$ cm.^{3}/g. and $B = 1\cdot0 + 0\cdot1$. No attempt has been made to estimate the intrinsic viscosity of sodium alginate dissolved in water, without added simple electrolytes, but measurements have been carried out (see, *e.g.*, Rose, *loc. cit.*) which showed that the ratio, defined by

$$\beta = \eta_{sp.} \text{ (without added electrolyte)}/\eta_{sp.} \text{ (in presence of simple electrolyte)} \quad (3)$$

is always larger than unity. These β values characterise the magnitude of the electroviscous effect.

In this paper the results of experiments are reported which enable a calculation to be made of the intrinsic viscosity of sodium alginate in solutions of sodium acetate, sulphate, phosphate, oxalate, fluoride, chloride, hydroxide, and carbonate. Experiments with the first five salts have not been previously published, but measurements with the last three electrolytes have already been described (*locc. cit.*). These previous tests were made with relatively dilute solutions of the simple electrolyte $Na^{+}_{y}X^{y-}$, and under these conditions a dependence of the intrinsic viscosity on the nature of X could not be established. We have now extended the concentration range of the simple electrolyte to 1N-solutions and could detect a specific anion influence, the occurrence of which is of relevance for a discussion of effects relating to the main topic of this series of papers (see following paper). Furthermore, the present measurements enable an estimate to be made of the average distance between the ends of the alginate chains. Similar calculations for this polyelectrolyte have not been reported elsewhere.

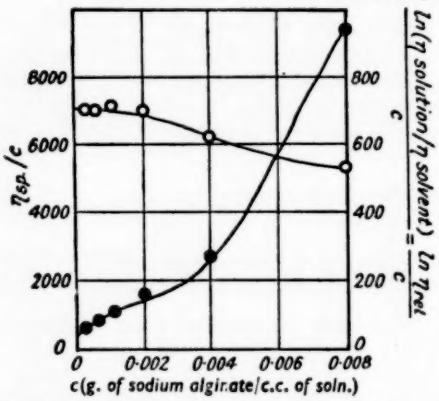
* The specific viscosity is defined by $\eta/\eta_0 - 1$ where η and η_0 are the viscosities of the solution and of the solvent, respectively.

Experimental

The sodium alginate, freed from traces of calcium by addition of sodium oxalate, was dialysed against 25% acetone–water and aliquots were dried as indicated on p. 494 of the preceding paper. Representative results of analyses, relating to a sample of number average molecular weight = $1{\cdot}2 \times 10^5$, were as follows: Na, $(4{\cdot}90 \pm 0{\cdot}10) \times 10^{-3}$; CO_2H, $(4{\cdot}71 \pm 0{\cdot}10) \times 10^{-3}$ g.-equiv./g. of dry gel. The absence of calcium was established by digesting the sodium alginate with concentrated nitric acid and testing the residue with ammonium oxalate.

At least one hour was allowed to lapse between preparation of the solution and measurement of the viscosity; control tests several hours later showed that the viscosity did not change to any detectable extent. Filtration of the sol through a glass filter was without influence on $[\eta]$. The sodium alginate was in the first instance dissolved in water, the required amount of the simple electrolyte, also dissolved in water, being added to the solution. A sufficiently accurate extrapolation of the ratio (1) to $c = 0$ could be done for all the alginate samples and simple electrolytes that have been tested by us, typical result being in the figure.† The various intrinsic viscosities are in the table. The results were obtained by using different sets of standard Ostwald viscometers, and Rose's observation (*loc. cit.*), that the viscosity depends on the rate of shear, was confirmed. The effect decreases with decreasing concentration and, in calculating the $[\eta]$ values listed in the table, an influence of the rate of shear, exceeding the specified experimental errors, could not be detected. The intrinsic viscosity of sodium alginate of number average molecular weight $7{\cdot}6 \times 10^4$ and $9{\cdot}8 \times 10^4$ was also determined, these measurements being done with solutions of the electrolytes indicated by an asterisk in the table. It could thus be established that the intrinsic viscosities could be represented by (2) with a B value which agreed within the limits of the experimental errors ($\pm 0{\cdot}15$) with that given on p. 497.

Estimation of intrinsic viscosity.



Solvent: 1N-Na_2SO_4 of pH6; solute: sodium alginate of number average molecular weight $1{\cdot}2 \times 10^5$. The black circles relate to the left ordinate, the open circles to the right ordinate. [For the method of plotting $\ln \eta_{rel.}$ against c, see, *e.g.*, Kraemer and van Natta, *J. Phys. Chem.*, 1932, **36**, 3175.] The $[\eta]$ values estimated from these two graphs are respectively 650 ± 100, and 690 ± 50 cm.³/g.; $t = 20°$. It should be noted that, by definition, the intrinsic viscosity is the value relating to the left-hand ordinates.

Intrinsic viscosities $[\eta]$ *of sodium alginate (of number average molecular weight* $1{\cdot}2 \times 10^5$*)* $(t = 20°)$*, and approximate distance between the chain ends of sodium alginate (of number average molecular weight* $9{\cdot}6 \times 10^4$*) in solutions of various simple electrolytes.*

Electrolyte and normality	$[\eta]$ (cm.³/g.)	$2R_0 \times 10^8$ (cm.) Eqn. (4)	Eqn. (5)	Electrolyte and normality	$[\eta]$ (cm.³/g.)	$2R_0 \times 10^8$ (cm.) Eqn. (4)	Eqn. (5)
N-NaCl *	870 ± 20	3·6	7·6	0·5N-$Na_2C_2O_4$ ...	620 ± 30	3·1	6·8
N-NaOH *	920 ± 100	3·7	7·8	0·6N-NaF	500 ± 40	2·7	6·3
N-NaOAc *	940 ± 50	3·8	7·8	0·1N-NaCl *	870 ± 40	3·6	7·6
N-Na_2CO_3 *	410 ± 50	2·5	5·9	0·1N-NaOH * ...	850 ± 50	3·6	7·6
N-Na_2SO_4	690 ± 50	3·2	7·0	0·1N-NaOAc * ...	870 ± 50	3·6	7·6
N-Na_3PO_4	620 ± 40	3·1	6·8	0·1N-Na_2CO_3 ...	690 ± 50	3·2	7·0

Measurements with all eight simple electrolytes listed in the table showed that the β values, defined by (3), are substantially larger than unity, as in the earlier experiments referred to above. With a sodium alginate sample of number average molecular weight $1{\cdot}2 \times 10^5$, for instance, and with 0·5—1N-solutions of the eight simple electrolytes listed in the table, we found that β was in the range 4·6—9·7 (20°).

† If the solutions are 1N. with respect to the permanent electrolytes, the slope of the $\eta_{sp.}/c$ versus c graphs depends markedly on the nature of the electrolyte.

Discussion

Debye and Bueche (*J. Chem. Physics*, 1946, **14**, 636; 1948, **16**, 573) deduced formulæ which can be written as follows:

$$[\eta] = 6\pi r_s R_s^3/10m \text{ [if } B \text{ in eqn. (2)} = 1] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$[\eta] = 4\pi R_s^3 \phi(\sigma)/3M \text{ [if } B \text{ in eqn. (2)} < 1] \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Here $[\eta]$ is the intrinsic viscosity, r_s is the radius of a spherical volume substituted for the base molecule, m is the mass of the base molecule, $2R_s$ is a distance which is approximately equal to the square-root of the average square of the distance between the chain ends,* M is the mass of the whole polymer, and $\phi(\sigma)$ is a quantity the value of which depends on that of the parameter B. (Similar correlations were deduced by a number of other authors, notably by W. Kuhn and H. Kuhn, *Helv. Chim. Acta*, 1943, **26**, 1442; 1947, **30**, 1234.)

The figures in cols. 4 and 8 of the table were calculated from (4), r_s being taken to be $4{\cdot}4 \times 10^{-8}$ cm. (cf. Astbury, *Nature*, 1945, **155**, 667). In order to show the influence of a variation of B on R_s, the values in cols. 4 and 8 were calculated by using (5), with $M = 1{\cdot}5 \times 10^{-19}$g and $B = 0{\cdot}84$ [$\phi(\sigma) = 0{\cdot}6$].

Equations (4) and (5) relate primarily to uncharged polymers. In the case of poly-electrolytes it has to be taken into account that the intrinsic viscosity depends also, to a certain extent, on the size of the counter-ion and on the thickness of the double layer formed by the simple electrolyte in conjunction with the poly-ion. It appears, however (cf. Kuhn, Kuenzle, and Katschalsky, *Helv. Chim. Acta*, 1948, **31**, 1994), that the contribution of the counter-ions to the intrinsic viscosity is small. If the correction is taken into account, the average distance between the ends of the alginate chains would be somewhat smaller than the figures given in cols. **3**, **4**, **7**, and 8 of the table. If an alginate chain of molecular weight 10^5 were fully extended, the distance between the chain ends would be more than 5 times larger than the largest value in cols. 4 and **8**. It can be concluded, therefore, that these poly-anions are curled, to a certain extent; *i.e.*, the main valency chains composed of repeating D-mannuronic acid residues are characterised by some internal flexibility.

Results of viscosity measurements (Pauli and Stenbach, *loc. cit.*; Fuoss and Strauss, *J. Polymer Sci.*, 1948, **3**, 216, 602, 603) and theoretical considerations (*e.g.*, Kuhn, Kuenzle, and Katschalsky, *loc. cit.*) make it probable that the shape of chain-like flexible macromolecules is dependent on the intramolecular electrostatic interaction between charged groups attached to the repeating units.† It appears probable, therefore, that sodium alginate, dissolved in water which is free from other electrolytes, is relatively extended, owing to the electrostatic repulsion of the carboxylate groupings. On addition of simple sodium salts, the tendency to form pairs between sodium and alginate ions will be enhanced, thereby decreasing the net charge of the poly-anion. This, in turn, appears to give rise to the formation of a self-curling system of greatly reduced viscosity, as shown by the numerical values of the ratio defined by (**3**). The electroviscous effect plays a rôle in solutions of sodium alginate which are 0·1—1N with respect to added electrolyte $Na^+_\nu X^{\nu-}$. The intrinsic viscosities, relating to the 0·1N-solutions, are not detectably dependent on the nature of X, but in 1N-solutions an influence of the anion obtains. One possible explanation involves the assumption that in 1N-solutions of $Na^+_\nu X^{\nu-}$ the dielectric constant of the reaction mixtures is so strongly modified by the nature of X as to bring about an alteration in the concentration of pairs between sodium and alginate ions to an extent sufficient to give rise to the actually observed viscosity changes.

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* H. Kuhn (*Experientia*, 1945, **1**, 28) showed that the shape of flexible chain-like molecules can be characterised by the average distance between the chain ends, $\bar{h}$, and by the "effective" length, $\bar{H}$, which equals $1{\cdot}5\bar{h}$. It follows, therefore, that $\bar{H} \simeq 3Rs$. This is mentioned in view of relationships to be discussed in the following paper.

† Meyer (*Biochem. Z.*, 1929, **214**, 253) was the first to discuss possible relationships between intramolecular electrostatic effects and the shape of chain-like polyelectrolytes.

96. *Influence of Ion Exchange on Optical Properties, Shape, and Elasticity of Fully-swollen Alginate Fibres.*

By J. L. Mongar and A. Wassermann.

On treatment of fully-swollen, stretched, and optically anisotropic calcium alginate fibres with solutions containing sodium ions, a cation-exchange reaction occurs, which is accompanied by an increase of volume and transparency of the gel, by a loss of birefringence, by axial contraction, and by increase of elasticity. An investigation into the mechanism of elastic deformation of sodium alginate threads is carried out and it is shown that shortening of stretched test pieces involves an increase of entropy. The type of cation exchange is established which is conducive to axial contraction and simultaneous radial swelling of various alginate fibres. An attempt is made to explain the observations from the point of view of changes of shape of chain-like alginate molecules.

Experiments already described (*J.*, 1952, 492) show that fully-swollen alginate fibres are cation-exchange materials. It is now established that some of these exchange reactions give rise to marked alterations in the macroscopic shape, optical behaviour, and elasticity of these gels. An attempt is made to show that ionic metatheses can be made responsible for a folding of initially straight segments of the chain-like alginate molecules, and that this, in turn, brings about the over-all alteration of the gel properties. The postulated internal flexibility of the macromolecules, here considered, and the influence of simple electrolytes on the degree of molecular folding, is in concordance with conclusions to be derived from the viscosity work described in the preceding paper.

Experimental

Materials.—In preparing sodium alginate fibres (see *J.*, 1952, 497) the volume and concentration conditions were adjusted in a manner to provide for complete removal of the calcium. The specific gravity of these gels was close to that of the suspension medium.

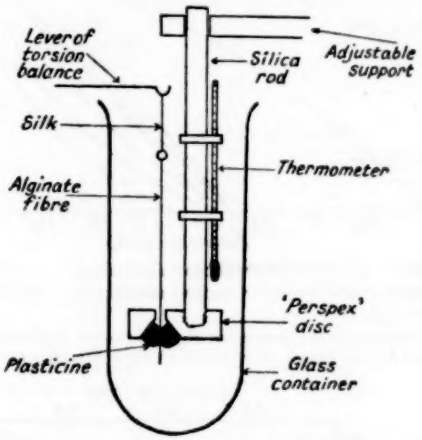
Viscosity of Magnesium Alginate.—The measurements were done as those described in the preceding paper.

Birefringence.—The relative retardation, or the distance by which the slow light wave lags behind the fast light wave in passing through an alginate gel, was measured with an optical system consisting of polarising and analysing nicols, compensator and accessory projection components, the light source being an electric lamp fitted with a daylight filter. The relative retardation could be calculated from the readings on the compensating disc, the tables for conversion being supplied with the instrument. In order to calculate the birefringence (relative retardation/unit thickness of fibre) the fibre diameter was determined either by focusing the microscope to the top and bottom of the fibre and measuring the change of position of the microscope tube, or else with a calibrated eye-piece scale in the ocular of the microscope. The measurements were done at room temperature (mostly 18—20°), the fibre being kept suspended in the relevant swelling medium.

Axial Contraction and Radial Swelling.—Fully swollen fibres were hung over a hook attached to the lever of a torsion balance, the length measurement being done with the help of a ruler, which was at a distance of 5—10 cm. from the fibre. Before being rinsed with the solution to be tested, the gel was treated with water until a single strand was formed. The length was 10 cm. in most experiments, and the accuracy of the length measurements of the fibre before ion exchange had taken place was $\pm 0{\cdot}2$ cm. Immediately after the initial rinsing with water, the electrolyte solution was passed over the fibre, at a rate of 2—5 cm.^{3}/min.; after known time intervals the flow was discontinued and the weight of the gel was quickly determined after its surface had been dried. In other experiments the fibre was placed in a container, the bottom of which was covered with mercury or with a layer of Vaseline. Length measurements were done with the help of a ruler floating alongside the gel in the solution to be tested, or by means of a travelling microscope. The fibre was kept straight by pushing it against the edge of the ruler or against that of a glass plate.

Elasticity.—One end of a fully-swollen alginate fibre was fixed by a weaver's knot to a silk thread which was connected with the lever of a torsion balance. A little Vaseline was applied to make the silk into a single strand, which was inextensible compared with the swollen gel. The other end of the alginate thread was fitted into a Perspex disc, supported by a silica rod, as shown in Fig. 1. The rod was fitted into an adjustable support by means of which it could be placed into a vessel containing the required suspension medium. The alginate fibre was slightly stretched at the beginning of the tests, a load of 20—50 mg. being applied. The length of the fibre measured from the weaver's knot to the top of the Perspex disc was 10 cm. The

FIG. 1.



glass container could be quickly removed from the position, shown in Fig. 1, and be replaced by another similar vessel, the position of the test piece being unaltered during this operation. Length changes were observed with the help of a travelling microscope focused to a pointer on the lever of the torsion balance. In determining the coefficients of thermal expansion, two glass containers I and II, filled with water or the electrolyte solution, were kept in thermostats the temperatures of which were respectively t_{I} and t_{II}. The container I was fixed in the position shown in Fig. 1 and the length of the alginate fibre was measured; the container was then quickly exchanged for II and the length measurements were repeated, care being taken to ensure that both sets of determinations related to steady states.

RESULTS

Elasticity.—Typical strain–stress curves of fully swollen calcium and sodium alginate fibres are shown in Figs. 2 and 3. In the former experiments 500 mg. were applied or removed every 10 sec.; and in the other tests, 100 mg. were applied or removed every 5 sec. These time scales were chosen for experimental convenience. A kinetic investigation of the elastic deformation has not been carried out, but it could be shown that the marked difference between the elastic properties of the two alginates cannot be due to the neglect of time effects. Fig. 2 shows that the first application of the load brings about a large amount of irreversible stretching, and the results of the second, third, and fourth cycles (the last is not shown in the figure) are reproducible, though not wholly reversible. These fibres become mechanically preconditioned, the effect being similar to that observed with other materials (see, *e.g.*, Leadermann, *Text. Res.*, 1941, **11**, 171). If the calcium alginate fibre is swollen in 5N-calcium chloride, instead of water, the first and subsequent cycles are similar. Mean elasticity moduli of " matured " fibres, estimated from the slope of such lines as those indicated by m, in the figures, are given in Table 1. The number average molecular weight of the sodium alginate, used for all the experiments, also for those described in the following sections, was $1{\cdot}0 \times 10^5$, unless otherwise specified. The fibre diameter (col. 1) relates to the unstretched fibres, and the moduli (E) in col. 5 were calculated with the help of these values. In view of the relatively large experimental errors of the moduli, the alteration of fibre diameter on stretching was not taken into account. The accuracy could be increased by carrying out tests with completely or partly dry gels; but such measurements

are of no relevance for the problems here considered. Attempts were made to measure the modulus of a sodium alginate fibre swollen in 1N-sodium chloride; under these conditions, the slipping was too large, however, to allow reproducible results to be obtained. In determining

FIG. 2. *The influence of load upon the elongation of fully-swollen calcium alginate fibres, of 0·2 mm. diameter and 10 cm. length, kept in water at 20°.*

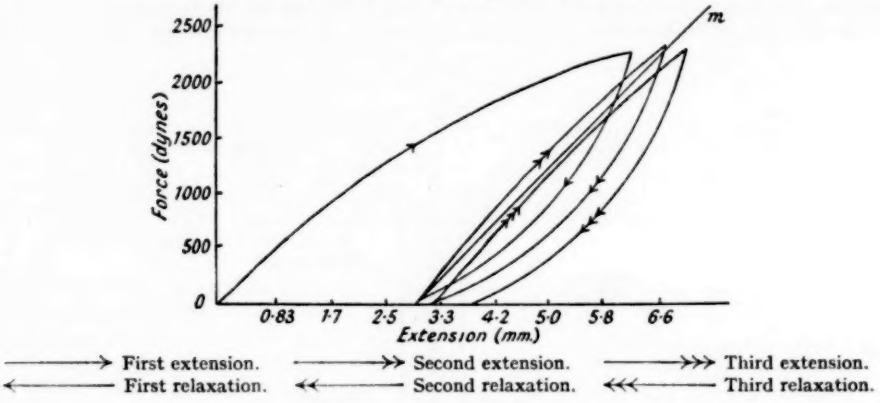
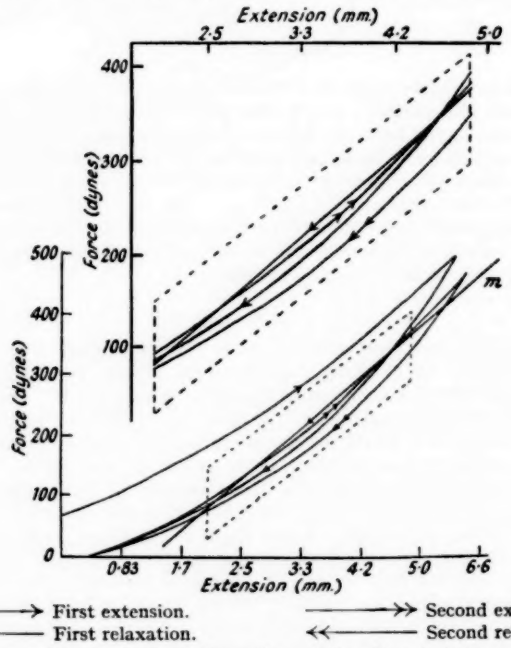


FIG. 3. *The influence of load upon the elongation of fully-swollen sodium alginate fibres, of 0·2 mm. diameter and 10 cm. length, kept in 5N-sodium chloride solution at 20°.*



(Only two cycles are shown; the load–elongation relationships in further cycles are similar to those represented by the graphs.)

the temperature–elongation relationships, at constant load, experiments such as those shown in Fig. 4 were carried out. A summary of these measurements is in the last column of Table 1. A negative sign of α indicates that the fibres shorten on increase of temperature. For a theo-

retical interpretation of these results it is of importance that the volume of sodium alginate gels does not significantly change, on deformation, if the temperature is constant. In the following two sections the results of further elasticity tests are mentioned. In these experiments the initial slope of the strain–stress curve was determined, elongations being usually up to about 1%.

TABLE 1. *Elasticity moduli, E, and linear coefficients of thermal expansion, α, of fully-swollen alginate fibres.*

Diam. (mm.)	No. of cycles	Temp. range	Load (mg.)	$10^{-8}E$ (dynes/cm.^{2})	$10^5\alpha$ (degrees^{-1})
		Calcium alginate fibre in water.			
0·18—0·23	4	20°		2·0 ± 0·5	
	22	9—33	500		+0·0 ± 0·1
	5	11—37	100		+0·2 ± 0·1
	3	10—44	100		+0·2 ± 0·2
	3	10—40	50		+0·5 ± 0·3
		Calcium alginate fibre in 5N-$CaCl_2$.			
	4	−7—22		4·0 ± 0·5	
	6	11—43	100		+0·5 ± 0·3
	6	10—46	500		+0·5 ± 0·3
	4	−15—15	500		0·0 ± 0·3
	3	−10—15	200		0·0 ± 0·3
		Sodium alginate fibre in 5N-NaCl.			
0·16—0·23	4	−7—22		0·25 ± 0·05	
0·41	6	20		0·15 ± 0·05	
0·18—0·23	27	5—45	50		−4·0 ± 0·5
	3	5—45	80		−4·2 ± 0·8
	24	5—45	100		−3·4 ± 0·5
	2	5—45	130		−2·7 ± 0·8
	14	5—45	150		−3·0 ± 0·6
	12	5—45	200		−2·4 ± 0·4
	14	5—45	250		−1·6 ± 0·4
	4	5—45	300		−1·2 ± 0·4
	5	−7—21	100		−8·6 ± 1
	7	−7—21	250		−4·2 ± 0·5
		Sodium alginate fibre in 2N-NaCl.			
0·2	4	20		0·10 ± 0·05	

Birefringence tests; effects accompanying the conversion of calcium alginate into the sodium salt. Fully-swollen, sufficiently stretched calcium alginate fibres are birefringent, the refractive index, n_1, in the direction of the length axis of the fibre being larger than that, n_2, perpendicular to this direction. Fig. 5 shows that the birefringence is approximately proportional to the reciprocal fibre diameter. The considerable deviations of some of the results from the straight line, shown in Fig. 5, are probably due, *inter alia*, to the fact that the birefringence of different sections of one and the same fibre is not always identical, and that the surface area of most gels is more birefringent than the core. In a test with a fully-swollen calcium alginate fibre, 0·4 mm. in diameter, the birefringence increased, on removal of gel water, from $1·0 \pm 0·1 \times 10^{-4}$ to $6·0 \pm 0·5 \times 10^{-4}$. Other tests showed that the birefringence of dried sodium and calcium alginate threads is similar, while fully swollen sodium alginate is optically isotropic. The graphs *A* and *E* in Fig. 6 show, moreover, that a replacement of the non-permeant calcium by sodium ions gives rise to a gradual disappearance of the optical anisotropy. These experiments were done with sodium chloride solution, but similar observations were made with other electrolytes. Calcium alginate fibres are opaque, but on conversion into mixed calcium sodium alginate, the gel becomes gradually transparent. If the permanent anion is chloride or acetate, the change of birefringence and transparency at the outside of the fibres is similar to the corresponding alterations near the core. If, however, solutions of sodium carbonate, sulphate, or phosphate are used, the birefringence near the outside of the fibre disappears before the whole fibre becomes optically isotropic. The outside portion becomes transparent while the birefringent interior remains opaque, the boundary being sufficiently sharp to measure the gradual increase of the depth of the non-birefringent layer with an accuracy of about 5%. The relationship between this depth and the degree of axial contraction is shown in Fig. 7, which relates to tests done with 1N-sodium carbonate.

FIG. 4.

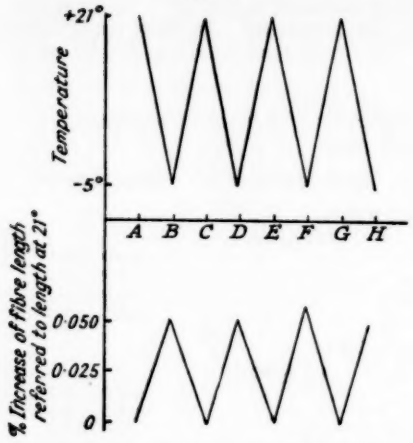


FIG. 5.

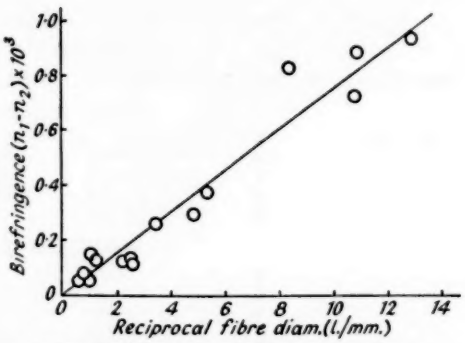


FIG. 4. Change of length of a fully-swollen sodium alginate fibre, of 0·18 mm. diameter and 10·0 cm. length, suspended in 5N-sodium chloride solution and stretched with a load of 100 mg. *A*, *B*, *C*, etc., indicate various heating and cooling cycles between the temperatures indicated in the ordinate of the upper part of the figure. The ordinate of the lower part of the figure indicates the % increase of fibre lengths, on cooling from 21° to − 5°, referred to the initial lengths of the test piece.

FIG. 5. Birefringence of fully-swollen calcium alginate fibres. The refractive indices n_1 and n_2 relate to daylight. The experimental error is indicated by the diameter of the circles.

FIG. 6. *Influence of ion exchange on various properties of alginate fibres.*

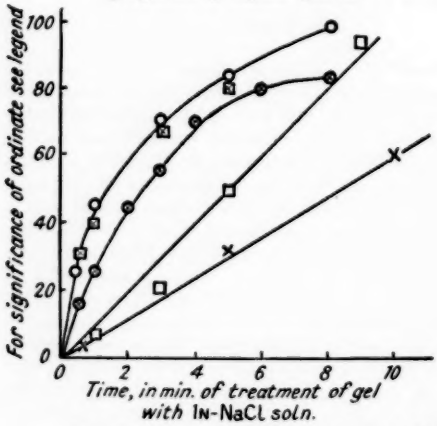


FIG. 7. *Loss of birefringence on contraction of calcium alginate fibres brought about by treatment with* 1N-*sodium carbonate.*

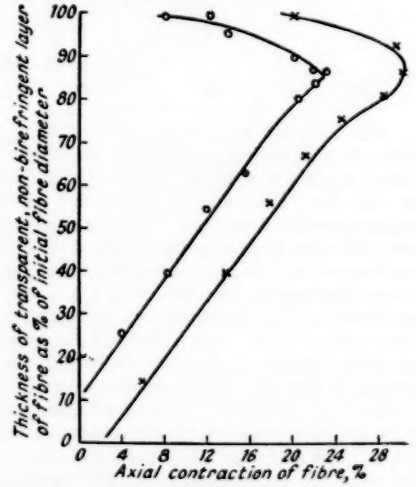


FIG. 6. The graphs relate to tests in which fully-swollen calcium alginate fibres, of 0·4—0·5 mm. diameter, were rinsed at 20° with 1N-sodium chloride solution.

□ = (A) = % Non-permeant calcium replaced by sodium ions.

⊗ = (B) = ‰ Decrease of length of fibre. × = (C) = % Increase of volume of gel.

□ = (D) = Increase of elasticity defined by $\frac{\text{Elasticity modulus of fully calcified fibre}}{\text{Elasticity modulus of mixed Ca–Na alginate}}$.

○ = (E) = % Decrease of birefringence.

FIG. 7. Diameter of fully-swollen calcium alginate fibre: O = 0·8 mm.; X = 1·1 mm.

On treatment of a calcium alginate thread, fully swollen with water, with 1N-calcium chloride no length or volume change could be detected. If, on the other hand, solutions containing sodium ions are used, the calcium–sodium ion exchange gives rise to marked axial contraction and simultaneous swelling, typical results being represented by the graphs *A*, *B*, and *C*, in Fig. 6. Graph *D* shows that the ion exchange is also accompanied by a considerable increase of elasticity. The error of these measurements is indicated by the size of the various symbols. Table 2 shows that the shape changes depend, under the specified concentration conditions, on the nature of the permeant anion, *e.g.*, chloride or carbonate. It has also been observed that the elasticity increases much more markedly on treatment with 1N-sodium carbonate than with 1N-sodium chloride, the degree of calcium–sodium ion exchange being similar in the two sets of experiments. In 0·1N-solutions, on the other hand, such specific anion effects could not be detected. Table 2 shows, furthermore, that relatively thin fibres, which had been stretched to a considerable extent during their preparation, alter their shape more markedly than thick fibres.

The rate of solution of sodium alginate, formed in these ion-exchange processes, is very small if the reaction mixture is 1N. with respect to sodium chloride, hydroxide, or acetate. In

TABLE 2. *Axial contraction and radial swelling of calcium alginate fibres, on treatment with solutions containing sodium ions.*

Ref. No.	Diam. of fibre before reaction (mm.)	Solution and concn. (g.-equiv./l.)	Increase of vol. of gel on maximum contraction, %	Increase of fibre radius on maximum contraction, %	Maximum axial contraction, %	Non-permeant Ca replaced, %
1	0·45	1N-NaCl	30 ± 3	20 ± 0·3	7·0 ± 0·5	100
2		1N-NaOH	40 ± 3	20 ± 0·3	5·0 ± 0·5	
3		1N-NaOAc	6 ± 1	10 ± 0·2	5·0 ± 0·5	
4		1N-Na_2CO_3	30 ± 3	30 ± 3	20 ± 1	12—15
5		1N-Na_2SO_4	5 ± 1	10 ± 0·2	6·0 ± 0·5	
6		1N-Na_3PO_4	35 ± 3	25 ± 0·3	16 ± 1	
7		0·5N-$Na_2C_2O_4$	40 ± 3	20 ± 0·2	4 ± 0·5	
8		0·5N-NaF	24 ± 2	20 ± 0·2	10 ± 1	
9	0·96	1N-NaCl	5 ± 1	3 ± 0·5	4·0 ± 0·5	100
10	0·28	1N-NaCl	90 ± 6	110 ± 10	10 ± 1	100
11	0·45	0·1N-NaCl	200	—	3 ± 0·5	90

the presence of the other sodium salts, listed in Table 2, and under the same concentration conditions, the sodium alginate dissolves within a few minutes. In runs Nos. 1—3 the axially contracted fibres remained mechanically coherent and the length did not alter for many hours; in Nos. 4—8, on the other hand, the final dissolution of the gel was preceded by a gradual lengthening of the shortened test piece (cf. also Fig. 7).

In order to find out whether the axial contraction is reversible, calcium alginate fibres, of 0·2 mm. diameter, were treated as follows. (1) The gel was saturated with 1N-calcium acetate; (2) the permanent electrolyte was washed out with water and the threads were placed in 2N-sodium chloride until maximum axial contraction was reached; (3) the non-birefringent gel was recalcified by bringing it into contact with 1N-calcium acetate. At the end of stage (3) some parts of the thread were slightly birefringent; the fibre was at this stage 7 ± 1% shorter than at the end of stage (1), but 3 ± 1% longer than at the end of stage (2).

Shape changes of various alginate fibres. These are indicated in Table 3; in these experiments the nature of both the non-permeant cation in the gel and the permeant ions in solution was varied. The pH of the solution was 12—13 in the runs with carbonates, tertiary phosphates, and hydroxides; 8·5—9 in tests with bicarbonates, secondary phosphates, citrate, or succinate; and 6—8 in the other experiments. A run with an oxalic acid–ammonium oxalate buffer of pH 5 was also done, a result similar to that at higher pH values being obtained. The fully swollen fibres (diameter 0·3—0·6 mm. in most tests), free from permeant electrolytes, were brought into contact with solutions of electrolytes, the concentration of which was 1N. unless otherwise specified. In run No. 9 the sodium carbonate was dissolved in 25% ethyl alcohol, and in No. 11 the calcium alginate fibres had been made from sodium alginate samples, the number average molecular weight of which was 4×10^4, 6×10^4, 8×10^4, and 1×10^5. Na_4ATP (in No. 10) is an abbreviation for the sodium salt of adenosine triphosphate.

Experiments 1—9. Axial contraction and simultaneous radial swelling of the alginate fibres could not be observed, this being indicated by the negative signs in lines 4 and 8 of the table.

If, for instance, a calcium alginate fibre is rinsed with 1N-hydrochloric acid (Expt. No. 1) until the calcium–hydrogen ion exchange is practically complete, the gel remains opaque, the extensibility does not alter to any marked extent, and the decrease in length and radius is respectively 4% and 18%. Similar observations were made on rinsing alginic acid fibres with 4N-calcium acetate, or calcium alginate fibres with 5N-aluminium sulphate. No shape changes occurred in runs Nos. 5, 6, and 7.

TABLE 3. *Influence of ion exchange reactions on the shape of various alginate fibres.*

Ref. No.	1	2	3	4	5
Alginate	Ca	H	Ba	Ca	Ca
Solution	HCl	$Ca(OAc)_2$ (4N)	HCl	$Al_2(SO_4)_3$ (5N)	$Cu(OAc)_2$
Axial contraction and radial swelling	—	—	—	—	—

Ref. No.	6	7	8	9	10
Alginate	Ca	Ca	Na	Mg	Ca
Solution	$AgNO_3$	$Ba(OH)_2$	HCl	Na_2CO_3	Na_4ATP (S); $NaHCO_3$ $Na_4P_2O_7$ (S); sodium citrate (S)
Axial contraction and radial swelling	—	—	—	—	+

Ref. No.	11	12	13	14	15
Alginate	Ca	Ca	Ca	Ca	Ca
Solution	K_2CO_3 (S); $KHCO_3$ K_3PO_4 (S); KH_2PO_4 KCl (3N)	$(NH_4)_2C_2O_4$ (S)	Li_2CO_3 (S) (0·3N)	RbOAc	CsCl
Axial contraction and radial swelling	+	+	+	+	+

Ref. No.	16	17	18	19	20
Alginate	Ca	Ca + Mg	Ca + Mg	Ca	H
Solution	Guanidinium carbonate (S)	Na_2CO_3 (S)	Na_2CO_3 (S)	$Mg(OAc)_2$	Na_2CO_3 (S); Na_2HPO_4 NaOH (S); NaF (S) Na_3PO_4 (S)
Axial contraction and radial swelling	+	+	+	+	+

Ref. No.	21	22	23	24	25
Alginate	H	Ag	Ag	Al	Al
Solution	K_2CO_3 (S); K_2HPO_4 KOH (S); KH_2PO_4	NaCl	K_2CO_3 (S); KCl	Na_2CO_3 (S)	K_2CO_3 (S)
Axial contraction and radial swelling	+	+	+	+	+

Ref. No.	26	27	28	29
Alginate	Ba	Cu^{++}	Cu^{++}	Cu^{++}
Solution	K_2CO_3 (S); K_2SO_4 (S)	K_2CO_3 (S); K_3PO_4 (S) KOH	Na_2CO_3 (S)	NH_3 (S)
Axial contraction and radial swelling	+	+	+	+

Experiments 10—29. These cation-exchange reactions led to simultaneous axial contraction and radial swelling, as indicated by the positive sign in the relevant lines of the table. The axial contraction was at least 3% (in many runs up to 20%), while the gel volume increased at least by 10%. In the tests with solutions containing the salts marked (S), the axially-contracted gel dissolved, the effect being similar to that mentioned in the preceding section. With the other salt solutions, however, the axially-contracted and radially-swollen gels remained coherent. In most runs the initially opaque gels became transparent and the elasticity modulus as well as the mechanical coherence decreased considerably, while the extensibility increased. When a copper alginate fibre was rinsed with 10N-potassium carbonate, the resulting gel could be elongated to twice its initial length, and after release the fibre returned to its original length to within $\pm 20\%$.

Experiments 9 *and* 19. These reactions involve magnesium alginate; for an interpretation of the results the following observations are of relevance. The viscosities of 0·1% aqueous solutions of magnesium and sodium alginate are similar; the elasticity modulus, ε, of a magnesium alginate fibre, fully swollen with 25% ethyl alcohol, is respectively 100, 50, and 6 times smaller than the E values of copper alginate, calcium alginate, and alginic acid threads; and on conversion of calcium alginate into the magnesium salt, the birefringence decreases to about 0·05 of its initial value.

Discussion

Calcium–Sodium Ion Exchange.—It can be assumed that the main valency chains in stretched calcium alginate fibres are attached to each other, in broadside-on positions, by salt bridges, *s*, operating between the bivalent calcium and the carboxylate groups of the polyanion. The formation of cross links implies that segments of adjacent alginate chains are relatively straight and approximately parallel to each other, and to the macroscopic fibre axis, this regular arrangement being responsible for the birefringence of the gels. The graphs in Fig. 6 and the results listed in Table 2 show that a replacement of calcium by sodium ions gives rise to the following effects: (1) Increase of fibre diameter, volume, and transparency of the gel; (2) loss of birefringence; (3) axial fibre contraction; (4) increase of elasticity. These observations are consistent with the model for calcium alginate specified above. The cation exchange will remove the lateral bonds, *s*, the univalent sodium not being capable of acting as cross-linking unit; and the devulcanisation can be made responsible for an increase of the distance between segments of adjacent main valency chains. The space thus made available will be filled with the outside solution * which, in

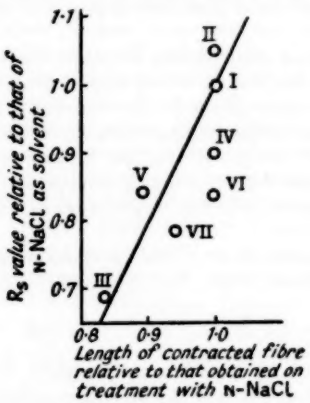


Fig. 8. *Functional relationship between the parameter* R_s, *as deduced from the intrinsic viscosity of sodium alginate, and the axial contraction of alginate fibres.* (The R_s values are those listed in cols. 3 and 7 of the table in the preceding paper; a similar functional relationship is obtained if the figures in cols. 4 and 8 are taken.)

I = 1N-NaCl; II = 1N-NaOH and 1N-NaOAc; III = 1N-Na_2CO_3; IV = 1N-Na_2SO_4; V = 1N-Na_3PO_4; VI = 0·5N-$Na_2C_2O_4$; VII = 0·5N-NaF.

turn, explains the effects (1). Further, the breaking of cross links will bring about a removal of geometrical restrictions imposed on the main valency chains, and it is reasonable to assume that the liberated chain segments will take up statistically more probable, folded configurations, and that these alterations of the molecular shape are responsible for the effects (2)—(4).

Some of the results in Table 2 show, however, that on treatment of calcium alginate threads with 0·1N-sodium chloride a substantial shortening in the direction of the length axis does not occur, although about 90% cation exchange had taken place. These observations indicate that a removal of lateral cross links is not a sufficient condition for conversion of stretched calcium alginate fibres into a self-curling system. It appears that a marked folding of the devulcanised segments takes place if an ionic atmosphere around the polyanion is created, which is capable of reducing the intramolecular electrostatic repulsion operating between the carboxylate groupings; and that this is brought about if the electrolyte concentration of the outside solution and of the gel phase is sufficiently high. In this connection it should be noted that some of the results, represented by the figure in the first paper of this series (p. 493), show that the relevant ratios characterising the distribution of sodium ions between the outside solution and calcium alginate are of the order of unity; and that the penetration of permeant sodium ions into the calcium alginate gel is much faster than the replacement of the non-permeant calcium (cf. Mongar and Wassermann,

* In the early stage of the interaction between calcium alginate and a relatively concentrated electrolyte solution, osmotic-pressure gredients must be operative, which could, in principle, give rise to a shrinking of the gel. As this has not been observed it is concluded that the diffusion of the electrolytes from the outside solution into the gel is fast, compared to the migration of gel water.

Discuss. Faraday Soc., 1949, **7**, 118). The influence of simple electrolytes on the overall length of partly or completely devulcanised alginate fibres can be compared with that responsible for the electro-viscous effect. The axial fibre contraction and the change of viscosity of sodium alginate, as shown by the numerical values of R_s given in the preceding paper, appear to be due to an interaction between simple electrolytes and the polyanion, which gives rise to a compression of hydrodynamic units of the main valency chains. This hypothesis is supported by the relationship represented in Fig. 8 which shows, on the whole, that those electrolytes which are capable of reducing the numerical value of the parameter R_s are also conducive to marked axial contraction of the alginate fibres. It is not surprising, of course, that the points in Fig. 8 do not fall on a smooth curve, or on a straight line. The R_s values were deduced from the results of tests done with dilute alginate sols, while the figures plotted on the abscissa of Fig. 8 relate to experiments in which the alginate concentration was considerably higher.

It can be regarded as further confirmation of the present hypothesis that those solutions, *e.g.*, 1N-sodium carbonate, which are conducive to strong axial contraction, also give rise to a marked increase of the elasticity; and that in tests with 0·1N-solutions of permeant electrolytes, neither the intrinsic viscosity nor the degree of axial contraction depends to any marked extent on the nature of the permeant anion.

Tests have been described which relate to the question of reversibility of contraction. During the recalcification of sodium alginate threads, under the specified experimental conditions, the formation of intramolecular salt bridges is more probable than during the first preparation of the calcium alginate threads, these materials having been stretched during the sol–gel transformation. Any intramolecular salt bridges which may be formed during the recalcification process will stabilise loops of folded main valency chains and, therefore, a full return to the original length and birefringence, without application of an external force, could hardly be expected.

Quantitative Interpretations of Some of the Elasticity Measurements.—This is done with the help of the following formulæ (cf., *e.g.*, Meyer and Picken, *Proc. Roy. Soc.*, 1937–38, [*B*], **124**, 29):

$$(\partial k/\partial T)_l = -(\partial \Delta S/\partial l)_T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which the temperature coefficient of a force, k, exerted by a deformed material in equilibrium, and at constant length, l, is related to the change of entropy, ΔS, accompanying the mechanical deformation. Over a small temperature range k may be taken to be a linear function of the absolute temperature, T, the curve $k = f(T)$ being replaced by its tangent, the equation of the resulting straight line being

$$k = a + bT \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The slope b is given by

$$b = (\partial k/\partial T)_l = -(\Delta l/\Delta T)_k/(\Delta l/\Delta k)_T \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where the two ratios on the right-hand side are obtained from some of the results listed in Table 1. The free energy change, ΔF, and the heat change, ΔH, characterising the mechanical deformation can be estimated from

$$(\partial \Delta F/\partial l)_T = k \text{ and } \Delta F = -\Delta H + T.\Delta S \quad . \quad . \quad . \quad . \quad . \quad (4)$$

In order to relate these thermodynamic quantities to one number average g.-mol. of the sodium alginate, the number of g.-equiv. in the test piece must be known. This quantity can be calculated from $dr^2\pi h/M_s$, where ρ is the specific gravity of the fully swollen fibre, r and h are respectively the fibre radius and length, both measured in cm., and M_s is the equivalent weight of sodium alginate. The signs of the α values in the first two sections of Table 1 indicate that calcium alginate fibres lengthen with increasing temperature, which implies a decrease of entropy on contraction of the stretched gels. The experimental errors of these measurements are so large, however, that numerical values of ΔS have not been calculated. The coefficients of thermal expansion of sodium alginate are listed in the last sections of Table 1; the values decrease with increasing load and temperature, the accuracy of each set of figures being between 15 and 30%. It should be noted that all the coefficients

of thermal expansion are negative; these gels, like rubber, shorten on increase of temperature. The measurements enable an approximate estimate to be made of the thermodynamic quantities ΔS, ΔF, and ΔH, which relate, however, only to sodium alginate fibres of 0·2-mm. diameter, fully-swollen with 5N-sodium chloride solution, under the specified load and temperature conditions; for instance, the modulus and the coefficient of thermal expansion being taken respectively as $0{\cdot}25(\pm 0{\cdot}05) \times 10^8$ dyne/cm.^{2} and $4{\cdot}0(\pm 0{\cdot}5) \times 10^{-5}$ degree^{-1}, it can be shown with the help of the above equations that the entropy increase accompanying an axial contraction of 5% of the length of the stretched fibre, amounts to $1{\cdot}5 + 0{\cdot}4$ cal./degree-g.-mol., *i.e.*, the term $T\Delta S$ of eqn. (4) equals $0{\cdot}4 \pm 0{\cdot}11$ kcal./g.-mol. at 20°. This value is smaller than the free-energy change, ΔF, which equals $2{\cdot}0 \pm 1{\cdot}0$ kcal./g.-mol. It appears, therefore, that the shortening of these stretched sodium alginate fibres involves an increase both of entropy and of heat content, ΔH being at least 0·45 kcal./g.-mol. For other load and temperature conditions the parameter b, estimated from eqn. (3), will be somewhat different; it can easily be verified, however, that in the whole range that has been tested, the increase of free energy, on contraction, is numerically larger than the term $T.\Delta S$. The main conclusion to be derived from these measurements relates to the sign of the coefficient of thermal expansion of these gels. The relevant deductions are independent of the numerical accuracy of ΔH or $T.\Delta S$.

The sign of the ΔS value, relating to sodium alginate fibres, can be explained as follows. In the stretched gel the main valency chains are extended, owing to an application of external force; on shortening, the macromolecules will curl, thereby giving rise to an entropy increase. The effect is comparable to that playing a rôle in the axial fibre contraction brought about by calcium–sodium ion exchange. In the calcium alginate thread the main valency chains are kept straight by lateral cross links, the removal of which will give rise to a statistically more probable configuration.

Other Cation-exchange Reactions.—It is of interest to find out whether axial fibre contraction, comparable to that accompanying the calcium–sodium ion exchange, occurs also in the cases of metatheses involving other cations, and the results of the relevant experiments are given in Table 3. The gels can be divided into class (1), which includes magnesium, ammonium, sodium, and potassium alginates, and class (2), which includes calcium, barium, copper, aluminium, and silver alginates and alginic acid. In the salts of the first class the intermolecular forces appear to be great enough to prevent a gel–sol transition in organic solvents, alcohol–water mixtures, or in aqueous solutions of certain electrolytes; if water is used, on the other hand, dissolution occurs. The undegraded gels of class (2) are different in that they swell only to a limited extent in water, or in all other solvents that have been tested, and it is concluded that this is due to salt bridges and oxygen–silver * or hydrogen bonds. Magnesium appears to act as a " unifunctional " ion in the gels here considered, as indicated by the solubility, viscosity, and low birefringence of magnesium alginate.

If fibres containing alginates of class (2) are suspended in solutions of bifunctional cations an ion exchange occurs, but the results of runs Nos. 1—7 of Table 3 indicate that this is not accompanied by axial contraction and simultaneous radial swelling. Another type of cation exchange, not conducive for such shape changes, occurs in runs Nos. 8 and 9, in which alginates of class (1) are suspended in solutions of bi- or uni-functional cations. If, however, solutions of unifunctional cations are brought in contact with fibres made from alginates of class (2), as in runs No. 10—29, a shortening of the test pieces without loss of gel water takes place. These effects can be explained with reference to a mechanism similar to that specified in the preceding sections, if one assumes that the rôle ascribed to the bi- and uni-valent calcium and sodium ions can be fulfilled by the other ions listed in Table 3.

In run No. 1 an exchange involving hydrogen ions occurs. The electrolytic dissociation of the alginic acid is repressed, under the conditions of this experiment, and thus the intramolecular electrostatic repulsion between the carboxylate groupings of the polyanion should decrease very markedly as a result of this ion exchange; it follows therefore, from

* Other compounds containing " bifunctional " silver are silver cyanide or oxalate. The terms " uni "- and " bi-functional " are used in the sense defined by Flory (*J. Amer. Chem. Soc.* 1941, **63**, 3091, 3296).

considerations mentioned above, that conditions ought to be particularly favourable for the curling of initially stretched chain segments. Axial contraction with simultaneous radial swelling and increase of transparency and extensibility could not be observed either in run No. 1 or in experiment No. 3, and it appears that the formation of lateral hydrogen bonds between adjacent chains prevents the expected alteration of the molecular shape. The relatively small axial contraction in run No. 1 can be accounted for by a loss of gel water, similar effects having been observed in reactions involving the interchange of bi- or ter-valent ions. This de-swelling is regarded as a salting-out effect which, in turn, may be due to alterations in the heat of swelling, caused by a dissolution of permeant electrolytes in the gel water. Such energy changes are similar to those described in the following paper. As a result of the partial collapse of the gel structure, a relatively large number of segments of adjacent chains may be situated in juxtaposition, thereby being prevented, for stereochemical reasons, from taking up positions of relatively high statistical probability. The increase of birefringence on de-swelling of alginates is perhaps also compatible with the assumption that the removal of gel water involves an increase of molecular orientation. These possibilities are pointed out in order to make it clear why the main deductions referred to in this section are based on the results of experiments in which the axial fibre contraction is accompanied by uptake of water from the outside solution.

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97. *Heat Effects Accompanying the Absorption of Simple Electrolytes by Fully-swollen Alginate and Cellulose Gels. A New Microcalorimetric Method.*

By I. L. MONGAR and A. WASSERMANN.

A microcalorimetric method is described which enables a determination of small heat effects accompanying the interaction of fully-swollen gels with solutions of permeant electrolytes. The results of the measurements enable a comparison to be made between the heat of swelling of alginate or cellulose gels in water and the heat of swelling of the same gels in sodium or calcium chloride solution. The thermochemical reactions here investigated represent typical examples showing the kind of energetic conditions conducive either to salting out or to salting in of colloids as brought about by addition of simple electrolytes.

THE measurements here described were carried out in order to estimate small heat changes which accompany the reversible interaction of fully-swollen alginate and cellulose gels with solutions of calcium and sodium chloride. The calorimetric technique employed is a modification of that used by Hill (see, *e.g.*, *Proc. Roy. Soc.*, 1938, *B*, **126**, 136) for a study of heat effects accompanying electrically stimulated contractions of frog sartorii. In our tests a thermopile served as a support for gels of dry weight between 0·0018 and 0·008 g.; the heat to be measured was liberated or absorbed on addition of 0·02—0·04 cm.^{3} of the salt solution. The results of these experiments enable a comparison to be made between the heat of swelling of the gel in water and in the electrolyte solution.

EXPERIMENTAL

The apparatus used is shown in Fig. 1. The thermopile, *G*, constructed by Downing, contained 60 iron–constantan couples in series; the well-insulated wire was 0·1 mm. thick, the resistance being 22 Ω and the sensitivity 3×10^{-3} volt/degree. Alginate gels or ash-free filter-paper strips, *E*, fully swollen with water, were hung over the upper silver electrode and held on to the lower electrode by a spring clip, *F*, made from Perspex. The two glass pipettes contained a solution of calcium or sodium chloride, introduced with the help of a hypodermic needle fitted to a precision

micro-syringe. One end of each of the pipettes, *D*, was connected with a flexible tubing, made from Polythene, which contained the same solution as the pipette; there was an air space on each side of the solution in the pipette, to prevent mixing with the solution in the flexible tubing, or a reaction with the gel. The glass vessel, *V*, filled with a paraffin–tetrachloroethylene mixture to the level *I*, was fitted to the rubber stopper, and was immersed in well-stirred water contained in a Dewar vessel. When temperature equilibrium was established, the two pistons, *C*, were pushed into the flexible tubing, thereby moving the solution from the pipettes to the gel on the thermopile. The movement of *C* was adjusted in such a way that the whole solution together with a portion of the air bubble behind it was expelled from the pipette. The heat changes accompanying the interaction of the electrolyte solution with the gel were measured by determining the deflection of a galvanometer connected with the thermopile by means of *A*.

FIG. 1. *Apparatus used for the measurement of heat effects accompanying the absorption of sodium and calcium chloride by fully-swollen alginate and cellulose gels.*

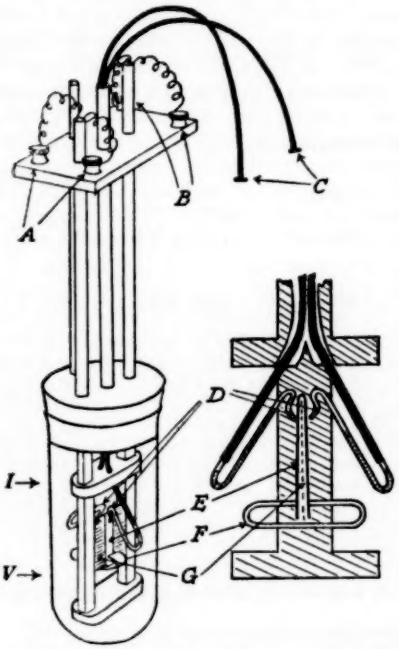
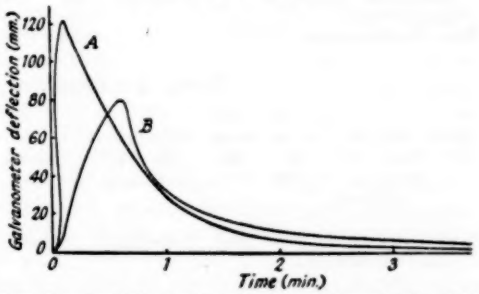


FIG. 2. *Typical galvanometer deflection–time curves at 19·5°.*



(*A*) *Curve relating to heat effect accompanying the addition of* 0·0400 *cm.*³ *of* 1N-NaCl *solution to* 0·022 *g. of fully-swollen calcium alginate fibres of* 0·02 *cm. diameter.*

(*B*) *Curve relating to electrically produced heat input of* $2{\cdot}31 \times 10^{-3}$ *cal.*

The sign of the galvanometer deflection in (*A*) *was opposite to that in* (*B*).

The removal of the solution from the pipettes takes less than 1 sec. Control experiments showed that the heat effect due to the passage of the solution through the jets is negligible. The liquid spread over the gel in a thin layer, the surface tension being sufficient to prevent an accumulation at the lower end, on top of the spring clip, provided the specific gravity of the paraffin–tetrachloroethylene mixture is suitably adjusted. After each experiment a calibration was carried out, by passing an alternating condenser discharge from *B* through the gel, the two silver electrodes serving as points of contact. A battery connected with a commutator, rotating at a rate of 184 r.p.m., charged and discharged a condenser ($2 \times 10^{-3}\mu$F; 49 volt) four times every revolution. Control tests established that the electrical heat input was proportional to the area under a curve obtained by plotting the time against the galvanometer deflection. Typical curves are shown in Fig. 2: curve *A* represents the deflection produced by the addition of 0·0400 cm.³ of 1N-sodium chloride solution to 0·022 g. of fully-swollen calcium alginate fibre of 0·2 mm. diameter; and curve *B* is the calibration curve. The sign of the galvanometer deflection was different in the two runs, heat being absorbed during the interaction of sodium chloride with the gel.

The ratio of the area under the two curves is 1·30; the heat input during calibration was

$2{\cdot}31 \times 10^{-3}$ cal., so the unknown heat effect can be calculated. The method of computation is possible because the galvanometer returns to its original position. If, on the other hand, the vessel, *V*, contained moist air, instead of the paraffin mixture, the initial and final galvanometer positions were markedly different. The effects responsible for the discrepancy are essentially those discussed by Hill ("Adventures in Biophysics," Philadelphia, 1931, Lecture I). Results showing the reproducibility of the micro-calorimetric method are in Table 1, and a summary of the results of the measurements is in Table 2.

The ΔH_d values in Table 2 are heats of dilution, which relate to the reaction between the sodium or calcium chloride solution and water in the absence of the gel, the amount of water used for this dilution process being equivalent to that absorbed by the fully-swollen gels used for these tests. The figure in the first line of col. 9, for instance, is the heat of dilution obtaining

TABLE 1. *Heat change accompanying the interaction of* 0·0400 *cm.*³ *of* 1N-*sodium chloride solution with* 0·022 g. *of fully-swollen calcium alginate fibre of* 0·02 *cm. diameter.* (Temp. 19·6°; heat input during calibration, $2{\cdot}31 \times 10^{-3}$ cal.)

Area (in cm.²) under curve obtained by plotting galvanometer deflection against time	Run	+53	+44	+50	+52	+66	+64	+49	+55
	Calibration	−43	−35	−40	−36·5	−39·5	−46	−30	−35
Heat of reaction (cal. $\times 10^{-3}$)		+3·0	+2·9	+2·9	+3·3	+3·8	+3·2	+3·8	+3·6

TABLE 2. *Results of heat measurements.*

Ref. No.	Gel on thermopile	Dry wt. of gel, mg.	Gel water, mg.	Electrolyte in soln.*	Temp.	No. of runs	$\Delta H_{exp.}$ (cal. $\times 10^{-3}$)	ΔH_d	$\Delta H_{exp.} - \Delta H_d$ (cal./g. dry gel)
1	Calcium alginate fibre †	1·76	20·2	1·0N-NaCl	19·6°	8	+3·31 ± 0·12	+2·9 ± 0·1	+0·2 ± 0·1
2	Calcium alginate strip ‡	1·76	20·2	1·0N-NaCl	20·0	17	+3·99 ± 0·16	+2·9 ± 0·1	+0·6 ± 0·1
3	Cellulose §	6·0	22·0	1·0N-NaCl	19·9	11	+2·86 ± 0·13	+2·2 ± 0·1	+0·12 ± 0·04
4		6·0	22·0	1·0N-NaCl	12·8	10	+3·83 ± 0·18	+5·5 ± 0·5	−0·28 ± 0·1
5		8·1	29·0	1·07N-$CaCl_2$	23·5	4	−3·5 ± 0·3	−1·9 ± 0·2	−0·20 ± 0·06
6	Calcium	2·24	30·0	2·13N-$CaCl_2$	20·0	5	−11·1 ± 0·5	−4·0 ± 0·2	− 3·2 ± 0·3
7	alginate	2·24	30·0	1·07N-$CaCl_2$	20·0	5	−6·8 ± 0·4	−1·7 ± 0·2	− 2·3 ± 0·3
8	fibre †	2·24	30·0	0·504N-$CaCl_2$	20·2	3	−2·4 ± 0·3	−0·79 ± 0·08	− 0·7 ± 0·2
9		2·24	30·0	0·106N-$CaCl_2$	23·8	2	−0·4 ± 0·1	−0·14 ± 0·02	− 0·3 ± 0·1
10		2·24	30·0	0·106N-$CaCl_2$	23·8	2	−0·4 ± 0·1	−0·14 ± 0·02	−0·12 ± 0·06
11	Calcium alginate strip ‡	4·3	54·0	1·07N-$CaCl_2$	25·6	3	−5·6 ± 0·6	−3·7 ± 0·1	− 0·4 ± 0·2

* 0·040 cm.³ of electrolyte solution were used in all runs except Nos. 3, 4, and 6, for which 0·02 cm.³ were used.

† Diameter 0·02—0·03 cm.; surface/volume ratio 100—250 $cm.^{-1}$.

‡ 0·2 cm. wide, 3·6 cm. long; surface/volume ratio 35 $cm.^{-1}$.

§ Whatman No. 41 filter-paper strips 0·2—0·25 cm. wide, 3·6 cm. long; ash content, <0·1%.

on addition of 0·0400 cm.³ of 1N-sodium chloride to 0·0202 cm.³ of water. It will be seen that the heat changes in cols. 8 and 9 relate to the actual quantities of gel used, while the figures in the last column relate to 1 g. of dry gel. An endothermic process is indicated by the plus sign, and a minus sign indicates that heat is liberated. The various ΔH_d values were calculated from the results published by Richards and Rowe (*J. Amer. Chem. Soc.*, 1921, **43**, 779), Richards and Dole (*ibid.*, 1929, **51**, 794), Robinson (*ibid.*, 1932, **54**, 1311), and Lange and Streek (*Z. physikal. Chem.*, 1931, *A*, **152**, 1). (Some of these authors use signs other than those employed in the present paper in order to indicate whether a reaction is exo- or endo-thermic.) It follows from the results of experiments (*J.*, 1952, 492) that the distribution ratios, ρ, are of the order of unity and that the interaction between calcium alginate and calcium or sodium chloride is wholly reversible, *i.e.*, the permeant electrolyte can be completely removed from the gel. It was also established that the cellulose used for runs 3—5 in Table 2 does not form a water-insoluble addition product with sodium or calcium chloride, and that, on addition of these salts, hydrogen ions are not released.

Discussion

The reaction between calcium alginate and sodium chloride solution (Ref. Nos. 1 and 2 in Table 2) involves cation exchange, and in the first set of measurements, in which thin fibres were used, a thermal effect due to the axial contraction of the test pieces may also play a role.* It can be shown with the help of a simple thermodynamic cycle that $\Delta H_{exp.}$, the experimentally determined over-all heat of reaction, is given by

$$\Delta H_{exp.} = \Delta H_d + \Delta H_s^{salt} - \Delta H_s^{water} + \Delta H_i + \Delta H_c \quad . \quad . \quad . \quad (1)$$

where ΔH_d is the heat of dilution of the electrolyte, in the absence of the gel, as defined above, ΔH_s^{salt} and ΔH_s^{water} are heats of swelling of the dry gels, the swelling medium being respectively the solution of sodium or calcium chloride and water, ΔH_i is the heat of calcium–sodium ion exchange, and ΔH_c is the heat of contraction of the fibres. The observations mentioned on p. 496 and in the preceding paper make it probable that on replacement of non-permeant calcium by sodium ions and on contraction of an alginate fibre heat is liberated. Numerical values of ΔH_i and ΔH_c, relating to the concentration conditions of the calorimetric measurements, cannot be estimated; it is merely possible to conclude that the difference between $\Delta H_{exp.}$ and ΔH_d, as listed in the first two lines of the last column of Table 2, is numerically smaller than the difference between ΔH_s^{salt} and ΔH_s^{water}. The interactions between cellulose and sodium or calcium chloride and between calcium alginate and calcium chloride, on the other hand, are relatively simple, because a significant cation replacement or an alteration of the shape of the gel does not occur. It is justifiable, therefore, to assume that in runs Nos. 3—11 of Table 2 the over-all heat, $\Delta H_{exp.}$, is given by the first three terms on the right-hand side of (1).

The reactions at 19·6—25·6° can be divided into two groups (*A*) and (*B*), according to whether the gels are brought into contact with sodium chloride or calcium chloride solution. In the former case, the sign of $\Delta H_{exp.} - \Delta H_d$ is positive, the numerical value of the difference being between 0·1 and 0·6 cal./g. of dry gel; and thus $\Delta H_s^{salt} - \Delta H_s^{water}$ is also a positive quantity. By taking into account the specified convention regarding thermochemical signs, it follows that a positive value of $\Delta H_s^{salt} - \Delta H_s^{water}$ indicates an interaction between the dry gel and the water which is energetically more favourable than that between the dry gel and the salt solution. In case (*B*), on the other hand, the difference $\Delta H_{exp.} - \Delta H_d$ is negative, the numerical values ranging from 0·1 to 3·2 cal./g. of dry gel. In these processes $\Delta H_s^{salt} - \Delta H_s^{water}$ must also be a negative quantity, and it can be deduced, therefore, that here the swelling in the salt solution is energetically more favourable than the swelling in water.

The two cases (*A*) and (*B*) can be regarded as representing typical examples showing the kind of energetic conditions conducive either for salting out or for salting in of certain colloids, as brought about by simple electrolytes.

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* The change in shape of the alginate strips, used in runs No. 2, is relatively small.

98. *Physical Properties and Chemical Constitution. Part XXIV.* Aliphatic Aldoximes, Ketoximes, and Ketoxime O-Alkyl Ethers, NN-Dialkylhydrazines, Aliphatic Ketazines, Mono- and Di-alkylaminopropionitriles, Alkoxypropionitriles, Dialkyl Azodiformates, and Dialkyl Carbonates. Bond Parachors, Bond Refractions, and Bond-refraction Coefficients.*

By ARTHUR I. VOGEL, WILLIAM T. CRESSWELL, GEORGE H. JEFFERY, and JAMES LEICESTER.

New measurements have been made of the refractivities at 20°, and the parachors of aliphatic aldoximes, ketoximes, and ketoxime *O*-alkyl ethers, *NN*-dialkylhydrazines, aliphatic ketazines, β-mono- and β-di-alkylaminopropionitriles, β-alkoxypropionitriles, dialkyl azodiformates and dialkyl carbonates, and the contributions of the :N·OH, :NO, N·NH_2, :N·N:, NH, N (tertiary), N:N, and CO_3 groups, and of O (from alkoxypropionitriles) have been evaluated. The bond refractions, as well as the bond parachors and the bond-refraction coefficients, have been computed for a large number of links with the aid of the experimental data given in this and previous papers of this series. The bond constants of several links have been deduced by a number of independent methods, and the results are in satisfactory agreement. The comprehensive table of bond refractions and bond parachors may be employed for the computation of "theoretical" refractions and parachors. The bond-refraction coefficients permit of the calculation of the refractive index (n_D^{20}) of a liquid compound from its chemical formula.

The structures of the esters of oxy-acids and of related compounds are discussed.

THE determination of atomic, group, and structural parachors and refractivities has been extended to a number of series of nitrogen-containing compounds (compare Eisenlohr, *Z. physikal. Chem.*, 1912, **79**, 412). New measurements of the densities and surface tensions over a range of temperatures as well as the refractive indices at 20° for the C, D, F, and G′ lines have been made and the constants calculated as in previous papers of this series.

TABLE 1. *Values for the* :N·OH *group from aldoximes and ketoximes.*

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
Aldoximes						
CHMe:N·OH	65·0	6·42	6·44	6·48	6·67	42·92
CHEt:N·OH	64·5	6·37	6·43	6·56	6·66	42·62
CHPr^n:N·OH	63·1	6·41	6·48	6·60	6·71	42·71
Mean :N·OH	64·2	6·400	6·450	6·546	6·680	42·75
Ketoximes						
CMeEt:N·OH	61·3	6·41	6·47	6·62	6·78	43·16
CMePr^n:N·OH	59·3	6·39	6·46	6·60	6·70	43·12
CEt_2:N·OH	58·5	6·33	6·41	6·53	6·64	43·16
CEtPr^n:N·OH	57·3	6·23	6·32	6·44	6·55	42·97
CPr^n:N·OH	54·9	6·22	6·29	6·42	6·53	42·81
Mean :N·OH	58·3	6·316	6·390	6·522	6·640	43·04

The constants for :NOH in aldoximes and ketoximes are collected in Table 1, and for :NO in ketoxime *O*-alkyl ethers in Table 2.

* Part XXIII, *J.*, 1948, 1833.

TABLE 2. *Values for the* :NO *group from ketoxime* O-*alkyl ethers.*

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
CMe_2:NOMe	53·5	5·67	5·74	5·87	6·01	41·91
CMe_2:NOEt	53·1	5·85	5·91	6·06	6·29	41·35
CMe_2:NOPr^n	52·2	5·70	5·78	5·91	6·04	41·52
CMeEt:NOEt	54·8	5·75	5·83	5·97	6·09	41·28
CMeEt:NOPr^n	47·7	5·53	5·60	5·74	5·89	41·52
CEt_2:NOEt	48·3	5·66	5·73	5·88	6·00	41·41
CEt_2:NOPr^n	48·1	5·58	5·64	5·80	5·92	41·50
CMePr^n:NOEt	49·3	5·79	5·85	5·99	6·12	41·45
CMePr^n:NOPr^n	48·6	5·64	5·70	5·84	5·98	41·48
CEtPr^n:NOEt	48·7	5·79	5·84	6·01	6·12	41·66
CEtPr^n:NOPr^n	47·8	5·71	5·76	5·93	6·03	41·42
CPr^n_2:NOEt	46·1	5·78	5·83	5·99	6·07	41·37
CPr^n_2:NOPr^n	46·0	5·78	5·82	5·98	6·10	40·56
Mean :NO	49·2	5·710	5·792	5·921	6·058	41·48

Four *NN*-dialkylhydrazines were prepared by the reduction of the appropriate dialkylnitrosamines. Zinc and acetic acid are satisfactory only for diethylnitrosamine (compare Fischer, *Annalen*, 1879, **199**, 287); the higher members of the series are most conveniently prepared by reduction of the nitrosamine with lithium aluminium hydride in dry ethereal solution. The constants for the $N{\cdot}NH_2$ grouping are given in Table 3.

TABLE 3. *Values for the* $N{\cdot}NH_2$ *group from* NN-*dialkylhydrazines*, $R_2N{\cdot}NH_2$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$NEt_2{\cdot}NH_2$	56·1	7·33	7·41	7·54	7·68	47·87
$NPr^n_2{\cdot}NH_2$	54·6	7·30	7·36	7·50	7·62	47·29
$NBu^n_2{\cdot}NH_2$	53·6	7·30	7·37	7·50	7·61	48·29
$NAm^n_2{\cdot}NH_2$	54·3	7·21	7·26	7·39	7·50	47·81
Mean $N{\cdot}NH_2$	54·7	7·285	7·350	7·483	7·602	47·82

Two more dialkylnitrosamines have been investigated and the constants for the N·NO grouping evaluated: these are in fair agreement with those found in Part XXIII (*J.*, 1948, 1838).

Values for the $N{\cdot}NO$ *group from nitrosamines*, $R_2N{\cdot}NO$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$NAm^n_2{\cdot}NO$	60·8	7·61	7·70	7·94	8·22	69·44
$N(n\text{-}C_6H_{13})_2{\cdot}NO$	59·6	7·74	7·83	8·12	8·36	69·29

The constants for the conjugated grouping :N·N:, evaluated from measurements on aliphatic ketazines, are collected in Table 4.

TABLE 4. *Values for the* :N·N: *group from aliphatic ketazines*, CRR':N·N:CRR'.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
CMe_2:N·N:CMe_2	63·8	8·09	8·25	8·57	8·86	39·11
CMeEt:N·N:CMeEt	61·4	8·06	8·21	8·55	8·83	38·80
CEt_2:N·N:CEt_2	55·9	7·90	8·08	8·39	8·69	38·83
CMePr^n:N·N:CMePr^n	58·6	8·09	8·21	8·56	8·87	39·02
CEtPr^n:N·N:CEtPr^n	53·0	7·99	8·18	8·50	8·91	38·91
CPr^n_2:N·N:CPr^n_2	49·2	8·13	8·30	8·61	8·91	39·06
Mean :N·N:	57·0	8·065	8·205	8·530	8·845	38·96

A series of β-monoalkylaminopropionitriles $NHR{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ has been prepared by the cyanoethylation of primary aliphatic amines. By subtracting the results for the corresponding nitriles $R{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ (Part XVII, *J.*, 1948, 674; *n*-heptyl and *n*-octyl cyanides in the present paper) the constants for the NH grouping are obtained directly: these are given in Table 5. The agreement, apart from the Mn_D^{20} figures which are somewhat higher, with the constants deduced from secondary aliphatic amines is reasonably satisfactory.

The constants for N (tertiary) were obtained in a similar manner from β-dialkylaminopropionitriles, prepared by the cyanoethylation of secondary aliphatic amines. The results are given in Table 6; the refractivities are slightly lower and the molecular-

refraction coefficients slightly higher than those already found for N from tertiary aliphatic amines (Part XXII, *J.*, 1948, 1827); the parachor contributions appear to decrease with increase in the molecular weight of the alkyl group.

TABLE 5. *Values for the* NH *group from* β*-alkylaminopropionitriles*, $NHR{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$NHEt{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	27·4	3·64	3·67	3·75	3·80	24·50
$NHPr^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	26·2	3·65	3·68	3·75	3·81	24·30
$NHBu^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	25·7	3·60	3·62	3·69	3·73	24·26
$NHAm^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	22·8	3·60	3·62	3·69	3·75	24·09
$n\text{-}C_6H_{13}{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	23·4	3·58	3·62	3·69	3·72	24·10
Mean NH	25·1	3·614	3·642	3·714	3·762	24·25
Mean NH (from NHR_2; *J.*, 1948, 1826)	28·4	3·572	3·610	3·667	3·732	23·34

TABLE 6. *Values for the* N *(tertiary) group from* β*-dialkylaminopropionitriles*, $NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	7·0	2·67	2·71	2·79	2·86	26·07
$NPr^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	4·1	2·58	2·60	2·69	2·78	25·63
$NBu^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	2·8	2·65	2·68	2·75	2·83	25·74
$NAm^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	1·0	2·59	2·62	2·69	2·76	25·53
Mean N (tertiary)	?	2·623	2·653	2·730	2·808	25·74
Mean N (from NR_3; *J.*, 1948, 1827)	7·2	2·698	2·744	2·820	2·914	24·37

The β-alkoxypropionitriles, prepared by the cyanoethylation of alcohols, may be employed to determine the constants for oxygen ($RO{\cdot}CH_2{\cdot}CH_2{\cdot}CN - R{\cdot}CH_2{\cdot}CH_2{\cdot}CN$). The results are given in Table 7: it will be noted that they are in reasonable agreement with those obtained for O in aliphatic ethers (Part XII, *J.*, 1948, 617).

TABLE 7. *Values for the* O *group from alkoxypropionitriles*, $RO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$MeO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	22·1	1·66	1·68	1·69	1·77	23·77
$EtO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	19·9	1·74	1·77	1·77	1·83	23·41
$Pr^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	20·0	1·74	1·75	1·79	1·83	23·22
$Bu^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	20·6	1·76	1·76	1·78	1·83	23·15
$Am^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	20·0	1·76	1·76	1·78	1·83	23·27
$n\text{-}C_6H_{13}{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	20·7	1·71	1·73	1·75	1·80	23·14
Mean O	20·4	1·73	1·74	1·76	1·81	23·33
Mean O (from R_2O; *J.*, 1948, 616)	19·8	1·753	1·764	1·786	1·805	22·74

The dialkyl azodiformates were used to compute the constants of the azo-group, N:N, by subtraction of the experimental figures for dialkyl oxalates (Part XIII, *J.*, 1948, 624). The refractive indices for the F and G′ lines could not be determined because of the deep colour of the liquids. The results are shown in Table 8.

TABLE 8. *Values for the* N:N *group from dialkyl azodiformates*, $RO_2C{\cdot}N{:}N{\cdot}CO_2R$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$EtO_2C{\cdot}N{:}N{\cdot}CO_2Et$	54·0	6·13	6·19	—	—	41·57
$Pr^nO_2C{\cdot}N{:}N{\cdot}CO_2Pr^n$	52·8	5·93	5·98	—	—	41·83
$Bu^nO_2C{\cdot}N{:}N{\cdot}CO_2Bu^n$	49·8	5·62	5·68	—	—	42·25
Mean N:N	52·2	5·893	5·950	—	—	41·88

Experimental data for a large number of dialkyl carbonates were required in connexion with the evaluation of certain bond constants (see below). The study of dialkyl carbonates (Part XXIII, *J.*, 1948, 1839) has therefore been extended to include a number of mixed alkyl carbonates as well as di-*n*-amyl and di-*n*-hexyl carbonates: all of these were synthesised from the pure chlorocarbonate and the appropriate alcohol. The constants for the CO_3 grouping are given in Table 9, and the mean values take into account *all* the carbonates investigated. The constants for the >CO grouping, derived with the aid of the data for acetals $CH_2(OR)_2$ (Part XII, *J.*, 1948, 617) are presented in Table 10: the new mean values, calculated for all the dialkyl carbonates, are in satisfactory agreement with the constants for the >C:O group for ketones (Part XI, *J.*, 1948, 611; Part XX, *J.*, 1948, 1816).

The comprehensive experimental data provided in this series of investigations have been employed to calculate bond constants. The advantages of the bond system as applied to refractions have been pointed out by Vickery and Denbigh (*Trans. Faraday Soc.*,

TABLE 9. *Values for the* CO_3 *group from dialkyl carbonates,* $RR'CO_3$.

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$EtPr^nCO_3$	83·1	7·71	7·74	7·82	7·87	86·21
$EtBu^nCO_3$	83·8	7·72	7·75	7·82	7·87	86·51
$EtAm^nCO_3$	81·3	7·74	7·79	7·86	7·92	86·35
$Et(n\text{-}C_6H_{13})CO_3$	82·0	7·77	7·81	7·88	7·93	86·37
$Pr^nBu^nCO_3$	82·6	7·69	7·71	7·78	7·82	86·64
$Am^n{}_2CO_3$	79·4	7·66	7·68	7·74	7·79	86·45
$(n\text{-}C_6H_{13})_2CO_3$	79·3	7·95	7·98	8·06	8·08	86·57
Mean CO_3 (including data in *J.*, 1948, 1839).....	82·0	7·712	7·745	7·811	7·864	86·40

TABLE 10. *Values for the* >CO *group from dialkyl carbonates,* CO(OR)(OR').

	P	R_C	R_D	R_F	$R_{G'}$	Mn_D^{20}
$EtPr^nCO_3$	45·4	4·47	4·49	4·54	4·56	41·25
$EtBu^nCO_3$	44·9	4·49	4·51	4·56	4·58	41·24
$EtAm^nCO_3$	44·1	4·50	4·53	4·58	4·61	41·29
$Et(n\text{-}C_6H_{13})CO_3$	44·3	4·55	4·58	4·60	4·64	41·32
$Pr^nBu^nCO_3$	44·1	4·48	4·50	4·55	4·57	41·35
$Am^n{}_2CO_3$	43·0	4·43	4·45	4·49	4·53	41·27
$(n\text{-}C_6H_{13})_2CO_3$	41·9	4·76	4·79	4·83	4·85	41·41
Mean >CO (including data in *J.*, 1948, 1840)...	44·3	4·480	4·505	4·545	4·574	41·26
Mean >C:O (ketones)	44·4	4·579	4·601	4·654	4·702	42·41

1949, **45**, 62) : these include (*a*) the assimilation into the bonds of the constitutive effects of the atomic system, which gives a neater scheme, and (*b*) the number of parameters is less for compounds containing more than one multivalent element, *e.g.*, for aliphatic amines, the atomic system uses five parameters (the atomic refractions of C and H, together with the three different values of N corresponding to primary, secondary, and tertiary amines) whereas the bond system employs only four parameters (the bond refractions of the C–C, C–H, C–N, and N–H bonds). We find that the bond system may be extended to include parachors and, rather unexpectedly, the molecular-refraction coefficients (Mn_D^{20}), leading to values for *bond parachors* and *bond-refraction coefficients*. The bond system may therefore be employed to evaluate the " calculated " parachors and the refractivities of compounds for the C, D, F, and G′ lines. The bond-refraction coefficients enable one to compute the refractive indices (n_D^{20}) of liquid organic compounds from their constitutional formulæ with an accuracy in most cases of 1% or better : the numerous practical applications of this facility are obvious (compare Vogel *et al.*, *Chem. and Ind.*, 1951, 376; Warrick, *J. Amer. Chem. Soc.*, 1946, **68**, 2455).

The fundamental bond constants (C–C) and (C–H),* deduced from the mean values for CH_2 derived from normal aliphatic hydrocarbons (Part IX, *J.*, 1946, 133; compare Part X, *J.*, 1948, 607), are :

	(P)	(R_C)	(R_D)	(R_F)	$(R_{G'})$	(Mn_D^{20})
(C–C)	4·30	1·286	1·296	1·301	1·328	12·86
(C–H)	17·85	1·669	1·676	1·693	1·704	3·87

Vickery and Denbigh (*loc. cit.*) have carried out an exhaustive analysis of the literature data on normal alkanes and find the refractions for the D-line to be (C–C) 1·296 and (C–H) 1·674.

To facilitate the calculation of the various bond constants, it is convenient to have available the constants of the alkyl groups. These have been computed from the data in Part IX (*loc. cit.*) and are collected in Table 11 [compare Table 1 in Part XI (*loc. cit.*)]. The bond constants for CH_3 were the mean values obtained by subtracting $(n-2)CH_2 + (C\text{–}C)$ from the normal alkanes; (C_2H_5) from $(CH_3) + CH_2$; $(C_3H_7{}^n)$ to $(C_8H_{17}{}^n)$ from $\{C_nH_{2n+2} - (C\text{–}C)\}/2$; $(C_9H_{19}{}^n)$ to $(C_{16}H_{33}{}^n)$ from $C_nH_{2n+2} - (C\text{–}H)$;

* Throughout the remainder of this paper, quantities in parentheses refer to bond constants.

($C_4H_9^s$), ($C_5H_{11}^i$). ($CHMePr^n$), and ($CHEt_2$) as for ($C_3H_7^n$) from the appropriate hydrocarbons; and ($C_3H_7^i$) from 2:5-dimethylhexane, $(CH_2Pr^i)_2 - 2CH_2 - (C{-}C)$.

TABLE 11. *Bond constants for alkyl groups.*

	(*P*)	(R_C)	(R_D)	(R_F)	(R_G)	(Mn_D^{20})
(CH_3)	53·30	4·993	5·004	5·070	5·084	11·70
(C_2H_5)	93·30	9·617	9·651	9·765	9·819	32·99
($C_3H_7^n$)	133·3	14·25	14·32	14·48	14·57	52·82
($C_3H_7^i$)	131·6	14·27	14·33	14·50	14·60	52·48
($C_4H_9^n$)	173·1	18·86	18·94	19·15	19·29	73·38
($C_4H_9^i$)	171·6	18·89	18·97	19·19	19·33	73·11
($C_4H_9^s$)	169·0	18·69	18·77	18·97	19·11	73·78
($C_5H_{11}^n$)	212·8	23·50	23·60	23·87	24·04	94·03
($C_5H_{11}^i$) *	210·4	23·45	23·55	23·81	23·99	93·87
($C_5H_{11}^i$) †	210·9	23·53	23·63	23·89	24·07	93·78
($CHMePr^n$)	207·6	23·25	23·35	23·65	23·78	94·40
($CHEt_2$)	206·4	23·17	23·28	23·52	23·69	94·52
($C_6H_{13}^n$)	252·9	28·08	28·21	28·51	28·72	114·67
($C_7H_{15}^n$)	293·6	32·75	32·90	33·26	33·51	135·32
($C_8H_{17}^n$)	333·5	37·32	37·49	37·89	38·17	156·00
($C_9H_{19}^n$)	372·9	41·99	42·17	42·64	42·90	176·37
($C_{10}H_{21}^n$)	412·1	46·61	46·82	47·34	47·70	197·04
($C_{11}H_{23}^n$)	452·8	51·25	51·47	52·03	52·43	217·64
($C_{12}H_{25}^n$)	492·2	55·78	56·03	56·63	57·07	238·32
($C_{13}H_{27}^n$)	532·7	60·47	60·73	61·40	61·86	258·90
($C_{14}H_{29}^n$)	573·6	65·12	65·42	66·12	66·64	279·63
($C_{15}H_{31}^n$)	613·5	69·68	69·99	70·75	71·32	300·30
($C_{16}H_{33}^n$)	653·5	74·25	74·59	75·38	75·96	320·99

* From di*iso*amyl prepared from *iso*amyl bromide (from Sharples synthetic *iso*amyl alcohol) and sodium.

† From di*iso*amyl prepared from *iso*amyl bromide (from Bisol fermentation *iso*amyl alcohol) and sodium.

The bond constants for the keto-group, (C=O), in aliphatic ketones RR'CO (Part XI, *J.*, 1948, 611) were deduced from the relation

$$(C{=}O) = E - \{(R) + (R') + 2(C{-}C)\}$$

where *E* is the observed parachor, molecular refractivity, or molecular-refraction coefficient. The results are collected in Table 12: the constants for the methyl ketones are slightly higher than those for the other ketones.

TABLE 12. *Values for* (C=O) *from aliphatic ketones*, RR'CO.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Methyl ketones						
Me_2CO	46·4	3·48	3·51	3·56	3·60	29·88
MeEtCO	44·3	3·39	3·43	3·45	3·51	29·70
$MePr^nCO$	42·8	3·33	3·34	3·38	3·42	29·50
$MeBu^nCO$	42·5	3·48	3·51	3·56	3·59	29·49
$MeBu^iCO$	43·0	3·56	3·59	3·63	3·66	29·25
$MeAm^nCO$	44·4	3·55	3·59	3·62	3·67	29·38
n-C_6H_{13}·COMe	40·9	3·46	3·49	3·54	3·55	29·38
n-C_7H_{15}·COMe	38·9	3·43	3·45	3·49	3·53	29·37
n-C_9H_{19}·COMe	—	3·44	3·46	3·50	3·58	29·57
Mean C=O (methyl ketones)	42·6	3·46	3·49	3·53	3·57	29·50
Dialkyl ketones						
Et_2CO	42·2	3·30	3·32	3·36	3·40	29·61
$EtPr^nCO$	42·1	3·37	3·40	3·43	3·56	29·47
Pr^n_2CO	39·9	3·27	3·27	3·30	3·36	29·28
$EtBu^nCO$	40·6	3·29	3·31	3·35	3·37	29·47
$EtAm^nCO$	40·0	3·23	3·25	3·28	3·30	29·43
n-C_6H_{13}·COEt	40·5	3·28	3·29	3·35	3·37	29·54
n-C_7H_{15}·COEt	40·3	3·29	3·31	3·34	3·38	29·37
Bu^n_2CO	39·2	3·27	3·29	3·32	3·34	29·42
Bu^i_2CO	39·8	3·40	3·43	3·47	3·48	28·90
Am^n_2CO	38·2	3·32	3·33	3·36	3·38	29·36
Mean (C=O)	40·3	3·30	3·32	3·36	3·39	29·39

The bond constants (C–O) for aliphatic ethers (Part XII, *J.*, 1948, 617) were readily computed from the expression :

$$2(C\text{–}O) = RR'O - (R) - (R')$$

those in aliphatic acetals (Part XII, *loc. cit.*) were obtained from the ethers derived from $CH_2(OR)_2$ and $CH_3{\cdot}CH(OR)_2$ by obvious methods. The results are given in Tables 13 and 14, respectively.

TABLE 13. *Values of* (C–O) *from aliphatic ethers*, RR'O.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Et_2O	12·7	1·58	1·60	1·62	1·64	17·84
Pr^n_2O	11·9	1·50	1·52	1·54	1·56	17·73
Pr^i_2O	13·0	1·52	1·53	1·53	1·55	17·42
Bu^n_2O	12·1	1·49	1·51	1·52	1·54	17·72
Am^n_2O	12·4	1·47	1·48	1·49	1·51	17·72
Am^i_2O *	12·5	1·57	1·59	1·60	1·62	17·10
Am^i_2O †	12·2	1·50	1·51	1·52	1·54	17·64
$(n\text{-}C_6H_{13})_2O$	12·1	1·53	1·53	1·55	1·57	17·67
$(n\text{-}C_7H_{15})_2O$	11·8	1·50	1·50	1·52	1·54	17·70
$(n\text{-}C_8H_{17})_2O$	12·1	1·56	1·56	1·58	1·61	17·67
$MeBu^nO$	12·2	1·53	1·54	1·55	1·58	18·00
$EtBu^nO$	12·1	1·55	1·57	1·58	1·60	17·76
$MeAm^nO$	12·3	1·51	1·52	1·53	1·56	18·01
$EtAm^nO$	12·2	1·54	1·55	1·56	1·59	17·76
$n\text{-}C_6H_{13}{\cdot}OMe$	12·0	1·51	1·53	1·54	1·56	17·99
$n\text{-}C_6H_{13}{\cdot}OEt$	11·8	1·54	1·55	1·57	1·60	17·73
$(CH_2Cl{\cdot}CH_2)_2O$	13·1	1·54	1·55	1·57	1·58	17·56
Mean (C–O) $_{ethers}$	12·4	1·53	1·54	1·55	1·57	17·71
$(CH_2{\cdot}CH_2{\cdot}OEt)_2O$	11·9	1·52	1·53	1·55	1·56	17·98
$(MeO{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2)_2O$	12·3	1·51	1·52	1·54	1·55	18·17

* From Bisol fermentation *iso*amyl alcohol. † From Sharples synthetic *iso*amyl alcohol.

TABLE 14. *Values of* (C–O) *from aliphatic acetals*, $CH_2(OR)_2$ *and* $CH_3{\cdot}CH(OR)_2$.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$CH_2(OMe)_2$	12·0	1·45	1·46	1·47	1·49	17·96
$CH_2(OEt)_2$	11·7	1·46	1·47	1·48	1·50	17·66
$CH_2(OPr^n)_2$	11·5	1·45	1·45	1·46	1·48	17·65
$CH_2(OPr^i)_2$	11·8	1·44	1·45	1·45	1·47	17·56
$CH_2(OBu^n)_2$	11·4	1·46	1·47	1·47	1·49	17·70
$CH_2(OBu^i)_2$	11·3	1·46	1·46	1·47	1·49	17·62
$CH_2(OAm^n)_2$	11·3	1·45	1·46	1·46	1·48	17·73
$CH_2(O{\cdot}C_6H_{13}{}^n)_2$	11·5	1·44	1·45	1·46	1·47	17·72
$CH_3{\cdot}CH(OMe)_2$	11·5	1·42	1·44	1·44	1·46	17·83
$CH_3{\cdot}CH(OEt)_2$	11·1	1·46	1·47	1·48	1·50	17·53
$CH_3{\cdot}CH(OPr^n)_2$	11·0	1·44	1·44	1·45	1·47	17·55
$CH_3{\cdot}CH(OBu^n)_2$	10·8	1·45	1·46	1·46	1·48	17·58
$CH_3{\cdot}CH(OBu^i)_2$	10·7	1·45	1·46	1·47	1·48	17·46
Mean (C–O) $_{acetals}$	11·3	1·45	1·46	1·46	1·48	17·66

The preliminary values for (C–O) in trialkyl orthoformates $HC(OR)_3$ (Part XXIII, *J.*, 1948, 1835) are collected in Table 15 : these do not differ appreciably from (C–O) from acetals.

TABLE 15. *Values of* (C–O) *from trialkyl orthoformates*, $HC(OR)_3$.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$HC(OEt)_3$	11·3	1·43	1·45	1·45	1·47	17·54
$HC(OPr^n)_3$	10·9	1·44	1·44	1·45	1·47	17·57
$HC(OBu^n)_3$	10·5	1·45	1·45	1·46	1·47	17·58
Mean (C–O) $_{orthoformates}$	10·9	1·44	1·45	1·45	1·47	17·56

An independent determination of $(C\text{–}O)_{ethers}$ is obtained by the comparison of the experimental figures for β-alkoxypropionitriles $RO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ (this paper) and those for nitriles $R{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ (Part XVII, *loc. cit.*). The results are given in Table 16 : these are in reasonable agreement with those deduced from dialkyl ethers (Table 13).

The large volume of experimental results for aliphatic carboxylic esters (Part XIII, *J.*, 1948, 624), and dialkyl carbonates (Part XXIII, *J.*, 1948, 1839) have been analysed as

follows. The (C–O) constants in dialkyl carbonates may be evaluated directly by comparison with the appropriate aliphatic carboxylic esters [no assumption is necessary as to the

TABLE 16. *Values of* (C–O) *from alkoxypropionitriles,* $RO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$, *and nitriles,* $R{\cdot}CH_2{\cdot}CH_2{\cdot}CN$.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$MeO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	13·2	1·48	1·49	1·50	1·54	18·32
$EtO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	12·1	1·52	1·54	1·54	1·58	18·14
$Pr^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	12·2	1·52	1·53	1·55	1·58	18·04
$Bu^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	11·9	1·53	1·53	1·54	1·58	18·01
$Am^nO{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	12·2	1·53	1·53	1·54	1·58	18·07
$n\text{-}C_6H_{13}O{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	12·5	1·52	1·52	1·53	1·57	18·00
Mean (C–O)	12·4	1·52	1·53	1·53	1·57	18·10

character of the bond between carbon and oxygen only, C⁻⁻O, although for dialkyl carbonates this has been shown to be (C=O)—Part XXIII, *J.*, 1948, 1840, and also Table 10 of the present paper]:

$$RO{\cdot}CO{\cdot}OR' - R{\cdot}CO{\cdot}OR' = (R) + (R') + 4(C{-}O) + (C{\dashv}O) - [(R) + (R') + 2(C{-}O) + (C{\dashv}O) + (C{-}C)]$$

or
$$2(C{-}O) = RO{\cdot}CO{\cdot}OR' - R{\cdot}CO{\cdot}OR' + (C{-}C)$$

The results of these calculations, the experimental figures for $R{\cdot}CO{\cdot}OR'$ of Part XIII (*loc. cit.*) being used, are presented in Table 17: for some unsymmetrical dialkyl carbonates, the experimental data for two isomeric esters were employed in the computations. The mean bond refractions for the C–O link suggest that it is of the acetal type.

TABLE 17. *Values of* (C–O) *from dialkyl carbonates,* $RO{\cdot}CO{\cdot}OR'$, *and aliphatic carboxylic esters,* $R{\cdot}CO{\cdot}OR'$.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$MeO{\cdot}CO{\cdot}OMe$	11·3	1·38	1·39	1·39	1·40	17·63
$EtO{\cdot}CO{\cdot}OEt$	12·0	1·41	1·42	1·42	1·43	17·53
$Pr^nO{\cdot}CO{\cdot}OPr^n$	11·7	1·39	1·40	1·40	1·42	17·71
$Bu^nO{\cdot}CO{\cdot}OB^n$	11·2	1·39	1·39	1·40	1·40	17·70
$EtO{\cdot}CO{\cdot}OPr^n$	12·2	1·43	1·43	1·46	1·46	17·61
	12·3	1·40	1·41	1·42	1·43	17·66
$EtO{\cdot}CO{\cdot}OBu^n$	11·7	1·40	1·41	1·42	1·43	17·63
	11·9	1·40	1·40	1·41	1·42	17·67
$EtO{\cdot}CO{\cdot}OAm^n$	11·3	1·42	1·44	1·45	1·46	17·73
$EtO{\cdot}CO{\cdot}OC_6H_{13}{}^n$	11·8	1·46	1·47	1·47	1·48	17·75
$Pr^nO{\cdot}CO{\cdot}OBu^n$	11·2	1·40	1·40	1·42	1·42	17·74
	11·3	1·41	1·41	1·42	1·43	17·72
Mean (C–O)	11·6	1·41	1·41	1·42	1·43	17·67
$(C{-}O)_{acetals}$	11·3	1·45	1·46	1·46	1·48	17·66
$(C{-}O)_{ethers}$	12·4	1·53	1·54	1·55	1·57	17·71

The constants for *both* the C–O and the C⁻⁻O link in aliphatic carboxylic esters may be deduced from the experimental data for these esters and those for the dialkyl carbonates. For dialkyl carbonates

$$RO{\cdot}CO{\cdot}OR' = (R) + (R') + (C{\dashv}O) + 4(C{-}O)$$

or
$$(C{\dashv}O) + 4(C{-}O) = RO{\cdot}CO{\cdot}OR' - [(R) + (R')] \quad . \quad . \quad . \quad . \quad (1)$$

for aliphatic monocarboxylic esters

$$R{\cdot}CO{\cdot}OR' = (R) + (R') + (C{\dashv}O) + (2C{-}O) + (C{-}C)$$

or
$$(C{\dashv}O) + 2(C{-}O) = R{\cdot}CO{\cdot}OR' - [(R) + (R') + (C{-}C)] \quad . \quad . \quad . \quad . \quad (2)$$

and for aliphatic dicarboxylic esters

$$RO{\cdot}OC{\cdot}[CH_2]_n{\cdot}CO{\cdot}OR = 2(R) + n(CH_2) + 2(C\overset{\cdot}{\sim}O) + 4(C{-}O) + 2(C{-}C)$$

or $$2(C\overset{\cdot}{\sim}O) + 4(C{-}O) = RO{\cdot}OC{\cdot}[CH_2]_n{\cdot}CO{\cdot}OR - [2(R) + n(CH_2) + 2(C{-}C)] \quad (2')$$

The simultaneous equations (1) and (2) enable $(C\overset{\cdot}{\sim}O)$ and (C–O) to be calculated.

The mean values deduced from all the data for carboxylic esters (excluding formates, acetates, oxalates, and malonates) in Part XIII (62 esters) and for all the dialkyl carbonates (Part XXIII and present paper—12 esters), together with the values for the two bond constants, are tabulated below.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Mean $(C\overset{\cdot}{\sim}O) + 4(C{-}O)$	86·16	9·008	9·051	9·116	9·198	99·30
Mean $(C\overset{\cdot}{\sim}O) + 2(C{-}O)$	63·51	6·162	6·189	6·248	6·308	64·13
Mean (C–O)	11·3	1·42	1·43	1·43	1·45	17·56
Mean $(C\overset{\cdot}{\sim}O)$	40·9	3·32	3·33	3·38	3·42	29·01
$(C{-}O)_{acetals}$	11·3	1·45	1·46	1·46	1·48	17·65
$(C{-}O)_{ethers}$	12·4	1·53	1·54	1·55	1·57	17·71
$(C{=}O)_{ketones}$	40·3	3·30	3·32	3·36	3·39	29·39

These results support the view that in the CO_2R group of aliphatic carboxylic esters, the bond constants are $(C{-}O)_{acetals}$ and $(C{=}O)_{ketones}$.

The bond constants (C–Cl), (C–Br), and (C–I) were computed from the data given in Part VIII (*J.*, 1943, 636; see also Part XIV, *J.*, 1948, 645) from alkyl halides, polymethylene dihalides, and alkyl monohalogenoacetates. Preliminary figures for (C–F) were obtained from alkyl fluorides (Part XIV, *loc. cit.*). The results are tabulated below.

TABLE 18. *Values for* (C–Cl) *from aliphatic monochloro-compounds.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(M_D^{20})
From alkyl chlorides						
Pr^nCl	58·4	6·51	6·53	6·61	6·68	56·21
Pr^iCl *	60·3	6·62	6·66	6·73	6·81	55·77
Bu^nCl	57·2	6·44	6·48	6·55	6·63	56·37
Bu^iCl	56·6	6·37	6·41	6·48	6·55	56·62
Bu^sCl *	60·5	6·70	6·74	6·83	6·89	55·55
Am^nCl	57·4	6·42	6·46	6·51	6·57	56·48
Am^iCl (from synthetic alcohol)	58·8	6·65	6·69	6·77	6·83	56·27
Am^iCl (from fermentation alcohol) ...	57·9	6·52	6·56	6·63	6·69	56·43
$CHMePr^nCl$ *	60·8	6·72	6·76	6·80	6·91	55·68
$CHEt_2Cl$ *	63·0	6·85	6·88	6·98	7·04	55·60
$n\text{-}C_6H_{13}Cl$	57·6	6·50	6·53	6·62	6·69	56·60
$n\text{-}C_7H_{15}Cl$	57·1	6·41	6·43	6·54	6·57	56·65
$n\text{-}C_8H_{17}Cl$	56·7	6·44	6·47	6·55	6·61	56·70
$n\text{-}C_9H_{19}Cl$	57·5	6·52	6·54	6·63	6·70	56·94
$n\text{-}C_{10}H_{21}Cl$	59·9	6·50	6·54	6·60	6·66	56·99
$n\text{-}C_{11}H_{23}Cl$	59·1	6·43	6·49	6·55	6·61	57·04
$n\text{-}C_{12}H_{25}Cl$	57·5	6·49	6·52	6·59	6·67	57·10
From polymethylene dihalides.						
$Cl{\cdot}[CH_2]_2{\cdot}Cl$	56·5	6·48	6·50	6·58	6·64	57·34
$Cl{\cdot}[CH_2]_3{\cdot}Cl$	56·8	6·40	6·43	6·51	6·56	57·40
From alkyl monochloroacetates and dialkyl succinates.						
$CH_2Cl{\cdot}CO_2Me$	55·9	6·46	6·49	6·57	6·62	57·03
$CH_2Cl{\cdot}CO_2Et$	56·5	6·52	6·56	6·65	6·69	56·99
$CH_2Cl{\cdot}CO_2Pr^n$	56·4	6·51	6·54	6·61	6·64	57·00
$CH_2Cl{\cdot}CO_2Bu^n$	56·4	6·46	6·50	6·56	6·62	57·11
Mean (excluding *)	57·4	6·48	6·51	6·58	6·64	56·80

TABLE 19. *Values for* (C–Br) *from aliphatic monobromo-compounds.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
From alkyl bromides						
EtBr	72·1	9·31	9·38	9·53	9·67	123·18
Pr^nBr	70·6	9·31	9·37	9·52	9·66	123·69
Pr^iBr *	73·5	9·56	9·63	9·79	9·93	122·86
Bu^nBr	70·7	9·33	9·39	9·55	9·68	123·93
Bu^iBr	72·5	9·48	9·55	9·70	9·82	123·50
Bu^sBr *	74·5	9·73	9·80	9·97	10·12	123·08
Am^nBr	70·3	9·31	9·39	9·52	9·66	124·27
Am^iBr (from fermentation alcohol)	69·7	9·27	9·34	9·50	9·63	124·08
Am^iBr (from synthetic alcohol)	72·2	9·50	9·57	9·72	9·92	123·96
$CHMePr^nBr$ *	73·3	9·55	9·62	9·74	9·92	123·41
$CHEt_2Br$ *	75·3	9·73	9·79	9·97	10·11	123·49
n-$C_6H_{13}Br$	70·4	9·34	9·39	9·56	9·70	124·33
n-$C_7H_{15}Br$	69·9	9·30	9·36	9·51	9·64	124·48
n-$C_8H_{17}Br$	70·3	9·35	9·41	9·57	9·70	124·57
n-$C_9H_{19}Br$	71·2	9·25	9·32	9·45	9·64	124·91
n-$C_{10}H_{21}Br$	72·5	9·45	9·52	9·66	9·80	124·86
n-$C_{11}H_{23}Br$	70·9	9·22	9·30	9·45	9·58	125·06
n-$C_{12}H_{25}Br$	74·1	9·43	9·49	9·65	9·77	125·10
n-$C_{14}H_{29}Br$	71·3	9·23	9·29	9·44	9·56	123·35
n-$C_{16}H_{33}Br$	72·2	9·31	9·38	9·53	9·66	125·45
From polymethylene dibromides						
$Br\cdot[CH_2]_2\cdot Br$	69·8	9·42	9·48	9·65	9·78	[130·41]
$Br\cdot[CH_2]_3\cdot Br$	70·4	9·18	9·24	9·40	9·51	[129·34]
From alkyl monobromoacetates and dialkyl succinates						
$CH_2Br\cdot CO_2Pr^n$	69·3	9·32	9·39	9·54	9·65	125·14
$CH_2Br\cdot CO_2Bu^n$	68·3	9·16	9·23	9·37	9·50	125·30
Mean (excluding *)	70·9	9·32	9·39	9·54	9·68	124·51

TABLE 20. *Values for* (C–I) *from aliphatic monoiodo-compounds.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
From alkyl iodides						
MeI *	93·6	14·11	14·25	14·58	14·88	205·70
EtI	93·3	14·45	14·55	14·89	15·21	203·82
Pr^nI	92·9	14·48	14·62	14·97	15·29	203·10
Pr^iI *	94·3	14·84	15·00	15·38	15·67	202·40
Bu^nI	91·5	14·41	14·55	14·90	15·21	202·63
Bu^iI	93·1	14·44	14·59 †	14·93	15·24	202·18
Bu^sI *	97·6	14·02	14·08	14·57	14·91	202·10
Am^nI	92·3	14·49	14·63	14·97	15·28	202·15
Am^iI (from fermentation alcohol)	91·8	14·52	14·66	15·01	15·31	201·86
Am^iI (from synthetic alcohol)	93·9	14·51	14·65	15·00	15·31	202·01
$CHMePr^nI$ *	94·2	13·83	13·98	14·32	14·69	201·92
$CHEt_2I$ *	95·7	14·01	14·16	14·56	14·91	202·13
n-$C_6H_{13}I$	92·9	14·53	14·66	15·02	15·32	201·88
n-$C_7H_{15}I$	93·0	14·54	14·67	15·02	15·33	201·52
n-$C_8H_{17}I$	92·2	14·49	14·62	14·99	15·30	201·55
$I\cdot[CH_2]_3\cdot I$	90·7	14·30	14·43	14·79	—	[218·54]
From alkyl monoiodoacetates and dialkyl succinates						
$CH_2I\cdot CO_2Pr^n$	93·3	14·41	14·54	14·90	15·19	203·82
$CH_2I\cdot CO_2Bu^n$	92·7	14·59	14·74	15·09	15·39	202·97
Mean (excluding *)	92·4	14·47	14·61	14·96	15·28	202·46

† R_D for Bu^iI in Part VIII, *J.*, 1943, 637, should be 33·56, not 33·66.

TABLE 21. *Values for* (C–F) *from alkyl fluorides.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Am^nF	28·8	1·38	1·39	1·36	1·36	28·32
n-$C_6H_{13}F$	29·1	1·48	1·47	1·47	1·48	28·15
n-$C_7H_{15}F$	27·1	1·37	1·37	1·35	1·36	28·24
n-$C_8H_{17}F$	27·8	1·57	1·58	1·58	1·58	28·37
Mean	28·2	1·45	1·44	1·44	1·45	28·27

The bond constants for the C=C bond were derived from the experimental figures for vinylacetates and for undecylenates, unsaturated aliphatic hydrocarbons, allylmalonates,

and allyl esters of aliphatic acids (Part XVI, *J.*, 1948, 659). The method of calculation is essentially an application of that employed in Part XVI (*loc. cit.*) :

$$\overline{P} = CR^1R^2{:}CR^3R^4 + 2H - CHR^1R^2{\cdot}CHR^3R^4;$$

For bond constants this may be written :

$$(C{=}C) = CR^1R^2{:}CR^3R^4 + 2(C{-}H) + (C{-}C) - CHR^1R^2{\cdot}CHR^3R^4$$

The results are collected in Table 22.

TABLE 22. *Values for* (C=C) *from aliphatic ethylenic compounds.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Vinylacetates, $CH_2{:}CH{\cdot}CH_2{\cdot}CO_2R$						
R = H	28·2	4·11	4·16	4·27	4·37	20·03
R = Me	29·0	4·11	4·16	4·27	4·35	19·97
R = Et	28·3	4·06	4·12	4·23	4·32	19·93
R = Pr^n	28·4	4·10	4·16	4·26	4·36	19·76
R = Bu^n	28·1	4·12	4·18	4·30	4·38	19·73
R = Am^n	27·6	4·09	4·15	4·26	4·34	19·66
Undecylenates, $CH_2{:}CH{\cdot}[CH_2]_8{\cdot}CO_2R$						
R = Me	29·6	4·19	4·24	4·36	4·44	19·70
R = Et	29·1	4·11	4·14	4·26	4·35	19·79
R = Pr^n	29·2	4·13	4·18	4·30	4·40	19·79
R = Bu^n	28·3	4·13	4·18	4·28	4·40	19·98
Unsaturated aliphatic hydrocarbons						
C_5H_{10}	26·9	4·16	4·20	4·33	4·45	19·23
C_6H_{12}	29·7	4·11	4·16	4·29	4·39	19·23
C_8H_{16}	28·3	4·17	4·24	4·35	4·46	19·08
$C_{10}H_{20}$	28·8	4·08	4·11	4·24	4·37	18·99
$C_{12}H_{24}$	28·8	4·12	4·16	4·30	4·40	19·12
$C_{14}H_{28}$	28·0	4·06	4·10	4·23	4·34	19·20
$C_{16}H_{32}$	29·0	4·13	4·17	4·32	4·40	19·19
Diallyl	28·9	4·16	4·20	4·32	4·41	18·94
Allylmalonates, $C_3H_5{\cdot}CH(CO_2R)_2$						
R = Me	28·4	4·12	4·18	4·29	4·38	20·07
R = Et	27·7	4·07	4·11	4·22	4·32	19·90
R = Pr^n	26·5	4·07	4·12	4·24	4·33	19·79
R = Bu^n	28·1	4·13	4·18	4·28	4·40	19·75
Allyl esters of aliphatic acids						
$CH_3{\cdot}CO_2{\cdot}C_3H_5$	29·2	4·03	4·09	4·20	4·28	19·75
$CH_3{\cdot}CH_2{\cdot}CO_2{\cdot}C_3H_5$	29·0	4·13	4·18	4·30	4·39	19·76
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2{\cdot}C_3H_5$	27·6	4·10	4·16	4·27	4·38	19·86
$(CH_2{\cdot}CO_2{\cdot}C_3H_5)_2$	29·3	4·20	4·25	4·36	4·44	20·34
Mean (C=C)	28·5	4·12	4·17	4·28	4·38	19·39

The experimental data for but-3-yne-1-carboxyates and dec-9-yne-1-carboxylates (Part XVII, *J.*, 1948, 674) were used to determine the constants of the terminal C≡C bond. The relation

$$(C{\equiv}C)_{terminal} = HC{:}CR + 4(C{-}H) + (C{-}C) - CH_3{\cdot}CH_2R$$

was used for calculating the constants given in Table 23.

TABLE 23. *Values for* (C≡C) *from acetylenic esters.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
But-3-yne-1-carboxylates, $CH{:}C{\cdot}[CH_2]_2{\cdot}CO_2R$						
R = Me	53·6	5·83	5·88	5·98	6·07	25·31
R = Et	53·1	5·84	5·89	5·98	6·10	25·18
R = Pr^n	53·0	5·87	5·92	6·01	6·11	24·87
R = Bu^n	52·5	5·91	5·95	6·05	6·15	24·77
Dec-9-yne-1-carboxylates, $CH{:}C{\cdot}[CH_2]_8{\cdot}CO_2R$						
R = Me	55·1	5·78	5·83	5·95	6·03	25·10
R = Et	53·6	5·73	5·77	5·87	5·97	25·05
R = Pr^n	53·4	5·76	5·81	5·93	6·02	25·03
Mean $(C{\equiv}C)_{terminal}$	53·5	5·82	5·87	5·97	6·07	25·04

The literature data for d_4^{20} and n_D^{20} (Henne and Greenlee, *J. Amer. Chem. Soc.*, **1945**, **67**, 484; Hennion and Banigan, *ibid.*, 1946, **68**, 1380; Campbell and O'Connor, *ibid.*, 1939, **61**, 2898; Campbell and Eby, *ibid.*, 1941, **63**, 2684) for acetylenic hydrocarbons were employed in the compilation of Tables 24 and 25. It will be noted that the mean bond refraction (D line) for (C≡C) (non-terminal) is appreciably higher than for (C≡C) (terminal).

TABLE 24. *Values for* (C≡C) (*terminal*) *from acetylenic hydrocarbons* (*literature data*).

	(R_D)	(Mn_D^{20})		(R_D)	(Mn_D^{20})
Pent-1-yne	5·84	23·71	Hepta-1 : 6-diyne	5·85	24·26
Hex-1-yne	5·84	23·76	Nona-1 : 8-diyne	5·84	24·30
Hept-1-yne	5·84	23·78	Mean $(C{\equiv}C)_{terminal}$	5·85	24·02
Oct-1-yne	5·89	23·75			

TABLE 25. *Values for* (C≡C) (*non-terminal*) *from acetylenic hydrocarbons* (*literature data*).

	(R_D)	(Mn_D^{20})		(R_D)	(Mn_D^{20})
Pent-2-yne	6·16	24·98	Non-3-yne	6·24	24·67
Hex-3-yne	6·27	24·79	Dec-5-yne	6·25	24·56
Oct-2-yne	6·14	25·06	Undec-5-yne	6·16	24·49
Oct-3-yne	6·29	24·75	Nona-2 : 7-diyne	6·36	25·40
Oct-4-yne	6·34	24·73	Mean $(C{\equiv}C)_{non\text{-}terminal}$	6·24	24·83

The constants for the C≡N bond have been deduced from the experimental data for aliphatic cyanides (Part XVII, *J.*, 1948, 676: *n*-heptyl and *n*-octyl cyanides, this paper) and are presented in Table 26.

TABLE 26. *Values for* (C≡N) *from aliphatic cyanides.*

	(P)	(R_C)	(R_D)	(R_F)	$(R_{G'})$	(Mn_D^{20})
MeCN	64·5	4·76	4·79	4·84	4·88	30·71
EtCN	63·8	4·78	4·81	4·86	4·89	30·16
Pr^nCN	62·8	4·81	4·82	4·88	4·91	29·98
Bu^nCN	61·3	4·79	4·81	4·86	4·89	29·88
Am^nCN	60·9	4·80	4·82	4·87	4·90	29·80
Am^iCN (ex Sharples synthetic alcohol)	61·8	4·85	4·88	4·93	4·97	29·87
n-$C_6H_{13}CN$	59·4	4·78	4·81	4·86	4·90	29·65
n-$C_7H_{15}CN$	58·1	4·75	4·77	4·82	4·84	29·62
n-$C_8H_{17}CN$	58·0	4·88	4·89	4·95	4·98	29·39
Mean (C≡N)	61·4	4·80	4·82	4·87	4·91	29·91
$[CH_2]_2(CN)_2$	63·9	4·66	4·68	4·71	4·71	29·99
$CH_2{:}CH{\cdot}CH_2{\cdot}CN$	61·4	4·49	4·50	4·54	4·55	30·29

The constants (C–C) in three-, four-, five-, and six-membered carbon rings were evaluated from the experimental data given in Part XVIII (*J.*, 1948, 1804) and Part XIX (*J.*, 1948, 1809) by appropriate adaptation of the relation:

$$\text{Ring constant} = \underbrace{CH_2{\cdot}[CH_2]_{n-2}{\cdot}C}R^1R^2 + 2H - CH_3{\cdot}[CH_2]_{n-2}{\cdot}CHR^1R^2$$

viz., n(C–C) for a ring of n carbon atoms

$$= \underbrace{CH_2{\cdot}[CH_2]_{n-2}{\cdot}C}R^1R^2 - CH_3{\cdot}[CH_2]_{n-2}{\cdot}CHR^1R^2 + [n-1](C\text{–}C) + 2(C\text{–}H)$$

Tables 27—30 contain the results of these calculations.

TABLE 27. *Values for* (C–C) *from three-carbon rings.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
*cyclo*Propanecarboxylic acid	9·0	1·48	1·50	1·52	1·55	11·38
Methyl *cyclo*propyl ketone	8·9	1·52	1·54	1·56	1·59	11·19
Methyl *cyclo*propanecarboxylate	8·8	1·48	1·50	1·52	1·54	11·26
Ethyl *cyclo*propanecarboxylate	8·5	1·47	1·49	1·50	1·53	11·30
n-Propyl *cyclo*propanecarboxylate	8·4	1·49	1·50	1·52	1·55	11·33
n-Butyl *cyclo*propanecarboxylate	8·3	1·49	1·50	1·52	1·55	11·25
n-Amyl *cyclo*propanecarboxylate	8·1	1·45	1·47	1·49	1·51	11·24
Dimethyl *cyclo*propane-1 : 1-dicarboxylate	8·4	1·50	1·50	1·53	1·54	11·37
Diethyl *cyclo*propane-1 : 1-dicarboxylate	8·0	1·48	1·49	1·52	1·53	11·22
Di-*n*-propyl *cyclo*propane-1 : 1-dicarboxylate	7·8	1·44	1·44	1·47	1·49	11·26
Mean (C–C) for three-carbon rings	8·4	1·48	1·49	1·52	1·54	11·28

TABLE 28. *Values for* (C–C) *from four-carbon rings.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
*cyclo*Butanecarboxylic acid	7·1	1·38	1·39	1·40	1·42	11·51
Methyl *cyclo*butanecarboxylate	6·8	1·36	1·38	1·38	1·41	11·45
Ethyl *cyclo*butanecarboxylate	6·9	1·36	1·37	1·38	1·41	11·44
n-Propyl *cyclo*butanecarboxylate	6·8	1·37	1·38	1·39	1·42	11·41
n-Butyl *cyclo*butanecarboxylate	6·9	1·38	1·39	1·40	1·42	11·43
n-Amyl *cyclo*butanecarboxylate	6·8	1·35	1·37	1·37	1·40	11·45
Dimethyl *cyclo*butane-1 : 1-dicarboxylate	6·9	1·37	1·38	1·39	1·41	11·49
Diethyl *cyclo*butane-1 : 1-dicarboxylate	6·7	1·35	1·36	1·37	1·40	11·47
Di-*n*-propyl *cyclo*butane-1 : 1-dicarboxylate	6·7	1·36	1·37	1·39	1·41	11·40
Di-*n*-butyl *cyclo*butane-1 : 1-dicarboxylate	6·6	1·35	1·36	1·37	1·39	11·43
Mean (C–C) for four-carbon rings	6·8	1·36	1·37	1·38	1·41	11·44

TABLE 29. *Values for* (C–C) *from five-carbon rings.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
*cyclo*Pentane	4·5	1·257	1·263	1·285	1·292	12·06
Methyl*cyclo*pentane	5·2	1·28	1·28	1·29	1·32	11·85
*cyclo*Pentene	5·4	1·20	1·21	1·22	1·24	[11·58]
3-Methyl*cyclo*pentene	5·2	1·26	1·26	1·29	1·29	[11·44]
*cyclo*Pentanol	5·3	1·24	1·25	1·26	1·28	12·01
Methyl *cyclo*pentyl ether	5·1	1·25	1·26	1·26	1·29	11·94
Ethyl *cyclo*pentyl ether	5·0	1·25	1·26	1·26	1·28	11·97
*cyclo*Pentyl formate	5·3	1·24	1·25	1·26	1·28	12·01
*cyclo*Pentyl acetate	5·5	1·26	1·27	1·27	1·30	12·02
Mean (C–C) for five-carbon rings	5·2	1·25	1·26	1·26	1·28	11·95
*cyclo*Pentanone	5·7	1·32	1·33	1·33	1·33	12·02
3-Methyl*cyclo*pentanone	5·6	1·31	1·31	1·30	1·35	11·91
*cyclo*Pentyl chloride	5·3	1·28	1·29	1·30	1·32	12·09
*cyclo*Pentyl bromide	5·6	1·30	1·31	1·32	1·34	12·54
*cyclo*Pentyl iodide	5·9	1·32	1·34	1·35	1·37	12·88

TABLE 30. *Values for* (C–C) *from six-carbon rings.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
*cyclo*Hexane	4·6	1·267	1·273	1·289	1·304	12·27
Methyl*cyclo*hexane	4·4	1·28	1·29	1·30	1·32	12·04
Di*cyclo*hexyl	4·3	1·25	1·25	1·27	1·28	12·34
*cyclo*Hexene	4·7	1·23	1·24	1·25	1·26	12·10
*cyclo*Hexanol	—	1·26	1·27	1·27	1·30	12·33
*cyclo*Hexyl methyl ether	4·6	1·26	1·27	1·27	1·30	12·25
Ethyl *cyclo*hexyl ether	4·4	1·26	1·27	1·27	1·30	12·27
*cyclo*Hexyl formate	4·5	1·25	1·26	1·27	1·29	12·30
*cyclo*Hexyl acetate	4·8	1·27	1·28	1·29	1·32	12·30
Mean (C–C) for six-carbon rings	4·5	1·26	1·27	1·28	1·30	12·24
*cyclo*Hexanone	5·4	1·28	1·29	1·30	1·31	12·33
2-Methyl*cyclo*hexanone	5·1	1·30	1·31	1·32	1·34	12·22
3-Methyl*cyclo*hexanone	4·7	1·27	1·29	1·29	1·32	12·23
4-Methyl*cyclo*hexanone	5·2	1·32	1·33	1·34	1·37	12·21
*cyclo*Hexyl chloride	5·3	1·34	1·35	1·35	1·38	12·37
*cyclo*Hexyl bromide	4·8	1·30	1·31	1·31	1·34	12·81
*cyclo*Hexyl iodide	3·9	1·32	1·34	1·35	1·37	13·60

The constants (O–H) in alcohols are readily derived from the observations upon aliphatic alcohols ROH (Part XX, *J.*, 1948, 1815) and are given in Table 31.

TABLE 31. *Values for* (O–H) *from Aliphatic Alcohols.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
MeOH	22·7	1·66	1·68	1·68	1·70	13·14
EtOH	21·3	1·70	1·71	1·72	1·74	12·70
Pr^{n}OH	19·7	1·68	1·68	1·70	1·71	12·77
Bu^{n}OH	20·6	1·71	1·72	1·72	1·73	12·50
Bu^{i}OH	18·8	1·66	1·66	1·67	1·67	12·59
Am^{n}OH	19·2	1·70	1·70	1·71	1·72	12·53
Am^{n}OH (synthetic)	—	1·66	1·67	1·68	1·68	12·58
n-C_6H_{13}·OH	—	1·64	1·64	1·67	1·66	12·50
n-C_7H_{15}·OH	—	1·60	1·60	1·61	1·62	12·36
n-C_8H_{17}·OH *	—	1·64	1·64	1·67	1·69	12·39
n-C_9H_{19}·OH	—	1·62	1·63	1·64	1·69	12·65
n-$C_{10}H_{21}$·OH	—	1·64	1·64	1·64	1·65	12·59
n-$C_{11}H_{23}$·OH	—	1·62	1·63	1·64	1·65	12·60
CH_2:CH·CH_2·OH	—	1·57	1·57	1·57	1·58	13·15
Mean (O–H)$_{alcohols}$	20·3	1·65	1·66	1·67	1·68	12·65
MeO·CH_2·CH_2·OH	21·5	1·65	1·66	1·67	1·68	12·65
EtO·CH_2·CH_2·OH	19·7	1·62	1·62	1·63	1·63	13·05
Bu^{n}O·CH_2·CH_2·OH	—	1·59	1·58	1·60	1·59	12·85

* The data for *n*-octyl alcohol (**463**; Part XX, *J.*, 1948, 1818) partially duplicate those for *n*-nonyl alcohol, **464**. The correct figures are n_C 1·42711, n_D 1·42927, n_F 1·43459, $n_{G'}$ 1·43853, Mn_D^{20} 186·12.

In the calculations of the constants for the O–H bond in aliphatic carboxylic acids (Part XX, *loc. cit.*) the relation

$$(O–H) = R·CO_2H - \{(R) + (C{=}O) + (C–O)_{acetals}\}$$

was employed; the results are collected in Table 32.

TABLE 32. *Values for* (O–H) *from aliphatic carboxylic acids.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Me·CO_2H *	20·0	1·74	1·74	1·77	1·77	10·68
Et·CO_2H	20·3	1·78	1·79	1·81	1·82	10·55
Pr^n·CO_2H	20·2	1·82	1·83	1·86	1·86	10·45
Pr^i·CO_2H	20·4	1·77	1·77	1·79	1·80	10·30
Bu^n·CO_2H	19·6	1·82	1·82	1·85	1·84	10·55
Bu^i·CO_2H	19·8	1·80	1·80	1·83	1·83	10·34
Am^n·CO_2H	—	1·81	1·80	1·83	1·83	10·62
n-C_6H_{13}·CO_2H	—	1·80	1·80	1·84	1·84	10·78
n-C_7H_{15}·CO_2H	—	1·81	1·81	1·85	1·84	10·71
Mean (O–H)$_{acids}$ (excluding *)	20·0	1·80	1·80	1·83	1·83	10·54

The constants (S–S) are readily deduced from the data on dialkyl disulphides (R·S·S·R — R·S·R: Part XXI, *J.*, 1948, 1820), those for (C–S) from dialkyl sulphides, and those for (S–H) from aliphatic thiols, with the aid of the previously determined values for (C–S). The results are in Tables 33—35.

TABLE 33. *Values for* (S–S) *from dialkyl disulphides.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$(SMe)_2$	50·8	7·95	8·02	8·21	8·39	54·53
$(SEt)_2$	49·6	8·05	8·14	8·30	8·48	54·13
$(SPr^n)_2$	49·6	8·04	8·11	8·30	8·47	53·85
$(SPr^i)_2$	50·1	8·02	8·06	8·28	8·42	53·98
$(SBu^n)_2$	48·4	8·10	8·15	8·35	8·49	53·65
$(SBu^i)_2$	48·0	7·91	7·98	8·14	8·33	53·49
$(SAm^n)_2$	47·6	8·12	8·21	8·41	8·57	53·44
$(SAm^i)_2$	48·3	7·97	8·04	8·23	8·41	53·53
Mean (S–S)	49·0	8·02	8·11	8·28	8·45	53·83

TABLE 34. *Values for* (C–S) *from dialkyl sulphides.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	$(Mn)_D^{20}$
SMe_2	28·3	4·52	4·56	4·64	4·72	32·90
SMeEt	27·7	4·51	4·55	4·61	4·72	32·85
SEt_2	27·5	4·58	4·61	4·71	4·81	32·75
$SMeBu^n$	26·9	4·54	4·58	4·66	4·77	32·93
$SMeBu^i$	27·3	4·56	4·60	4·67	4·76	32·80
SPr^n_2	26·2	4·49	4·58	4·67	4·75	32·84
SPr^i_2 *	27·3	4·68	4·74	4·80	4·90	32·58
$SEtBu^n$	27·0	4·60	4·65	4·73	4·82	32·81
SBu^n_2	26·6	4·55	4·59	4·67	4·76	32·90
SBu^i_2 *	25·6	4·63	4·67	4·81	4·83	32·72
SBu^s_2 *	26·4	4·76	4·80	4·90	4·99	32·32
SAm^n_2	25·7	4·55	4·59	4·67	4·75	32·91
SAm^i_2	26·1	4·64	4·69	4·77	4·85	32·76
$S(n\text{-}C_6H_{13})_2$	25·4	4·62	4·66	4·75	4·83	32·94
$S(n\text{-}C_7H_{15})_2$	25·7	4·61	4·64	4·73	4·79	32·97
$S(n\text{-}C_8H_{17})_2$	25·5	4·56	4·59	4·69	4·76	32·98
Mean (C–S) (excluding *)	26·6	4·57	4·61	4·70	4·78	32·84

TABLE 35. *Values for* (S–H) *from aliphatic thiols.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	$(Mn)_D^{20}$
EtSH	44·1	4·73	4·76	4·84	4·92	23·82
Pr^nSH	42·6	4·76	4·79	4·87	4·94	23·70
Pr^iSH	43·7	4·54	4·57	4·63	4·88	22·69
Bu^nSH	41·8	4·81	4·84	4·90	4·99	23·87
Bu^iSH	41·6	4·77	4·80	4·86	4·93	23·75
Am^nSH	41·8	4·77	4·79	4·86	4·94	23·88
Am^iSH	42·5	4·76	4·80	4·86	4·93	23·80
$n\text{-}C_6H_{13}\cdot SH$	41·9	4·76	4·80	4·88	4·93	23·85
$n\text{-}C_7H_{15}\cdot SH$	—	4·72	4·74	4·82	4·85	23·66
$n\text{-}C_8H_{17}\cdot SH$	—	4·86	4·89	4·97	5·03	23·82
Mean (S–H) (excluding *)	42·1	4·77	4·80	4·87	4·94	23·79

The most trustworthy values for (C–N) and (N–H) in aliphatic amines are derived from the experimental data for primary and secondary aliphatic amines. Thus for primary amines

$$(C\text{–}N) + 2(N\text{–}H) = RNH_2 - (R)$$

and for secondary amines

$$2(C\text{–}N) + (N\text{–}H) = R_2NH - 2(R)$$

These two simultaneous equations give the values for the individual bond constants (C–N) and (N–H). The final results for primary and secondary aliphatic amines are given in Table 36.

TABLE 36. *Values for* (C–N) *and* (N–H) *from primary and secondary aliphatic amines.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	$(Mn)_D^{20}$
(C–N) + 2(N–H) *from primary aliphatic amines*						
NH_2Pr^n	46·3	5·11	5·13	5·21	5·28	29·24
$NH_2\cdot Bu^n$	45·5	4·99	5·02	5·09	5·15	29·08
$NH_2\cdot Bu^i$	45·0	4·98	5·01	5·07	5·13	29·07
$NH_2\cdot Am^n$	46·7	5·08	5·12	5·18	5·24	28·99
$NH_2\cdot Am^i$	46·6	5·05	5·09	5·17	5·21	28·97
$n\text{-}C_6H_{13}\cdot NH_2$	46·5	5·06	5·08	5·16	5·23	28·82
$n\text{-}C_7H_{15}\cdot NH_2$	—	5·04	5·06	5·12	5·19	28·81
$n\text{-}C_8H_{17}\cdot NH_2$	—	5·11	5·14	5·22	5·30	28·71
$CH_2{:}CH\cdot CH_2\cdot NH_2$	45·3	5·08	5·11	5·17	5·24	[29·94]
$NH_2\cdot CH_2\cdot CH_2\cdot NH_2$	47·8	5·11	5·13	5·19	5·26	29·57
Mean (C–N) + 2(N–H)	46·2	5·061	5·089	5·158	5·223	29·03

TABLE 36.—(*continued*)

2(C–N) + (N–H) *from secondary aliphatic amines, etc.*						
$NHEt_2$	33·7	4·95	5·00	5·07	5·19	36·82
$NHPr^n_2$	32·3	4·86	4·87	4·95	5·05	36·53
$NHPr^i_2$	33·2	4·96	4·98	5·04	5·17	35·87
$NHBu^n_2$	32·5	4·89	4·94	5·00	5·10	36·46
$NHBu^i_2$	32·4	4·85	4·89	4·96	5·04	35·88
$NHAm^n_2$	33·0	4·74	4·79	4·84	4·93	36·42
$NHAm^i_2$	31·7	4·71	4·76	4·83	4·90	36·30
$NH(C_6H_{11})_2$	34·7	4·95	4·99	5·06	5·14	35·97
$NHMe{\cdot}CO_2Et$	31·9	4·73	4·79	4·85	4·93	[38·30]
$NHEt{\cdot}CO_2Et$	31·3	4·89	4·93	4·99	5·08	[38·05]
Mean 2(C–N) + (N–H)	32·67	4·853	4·894	4·959	5·053	36·28
(C–N)	6·4	1·548	1·566	1·587	1·628	14·51
(N–H)	19·9	1·757	1·762	1·786	1·798	7·26

The constants for the C–N link have also been computed from the data on tertiary aliphatic amines (Part XXII, *J.*, 1948, 1827) and on β-dialkylaminopropionitriles {3(C–N) = $R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CN - 2(R) - CH_3{\cdot}CH_2{\cdot}CN + (C–H)$} and are tabulated in Tables 37 and 38, respectively. The results obtained directly from the tertiary amino-compounds are (apart from the parachors, which seem to lead to slightly lower constants) in satisfactory agreement with those given in Table 36.

TABLE 37. *Values for* (C–N) *from tertiary aliphatic amines.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn^{20}_D)
NEt_3	5·6	1·59	1·61	1·64	1·69	14·97
NPr^n_3	4·4	1·56	1·57	1·60	1·66	14·86
NBu^n_3	4·2	1·54	1·56	1·59	1·63	14·95
NAm^n_3	4·5	1·48	1·50	1·52	1·56	14·88
NAm^i_3	3·8	1·46	1·48	1·51	1·54	14·81
Mean (C–N)	4·5	1·53	1·54	1·57	1·62	14·89

TABLE 38. *Values for* (C–N) *from β-dialkylaminopropionitriles.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn^{20}_D)
$NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	4·1	1·54	1·56	1·59	1·63	15·07
$NPr^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	3·2	1·51	1·52	1·55	1·59	14·92
$NBu^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	2·8	1·53	1·55	1·57	1·61	14·96
$NAm^n_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	2·1	1·51	1·53	1·55	1·59	14·89
Mean (C–N)	3·1	1·52	1·54	1·57	1·61	14·96

We have also obtained values of the (N–H) constants from monoalkylaminopropionitriles, $R{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CN$, and alkyl cyanides, $R{\cdot}CH_2{\cdot}CH_2{\cdot}CN$. The constants for the C–N bond employed in the calculations were those determined from the β-dialkylaminopropionitriles (Table 38); these are slightly lower than those deduced from primary and secondary aliphatic amines (Table 36) and since two C–N bonds are involved, the differences will be expected to be larger. The results are given in Table 39.

TABLE 39. *Values for* (N–H) *from β-alkylaminopropionitriles.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn^{20}_D)
$NHEt{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	25·5	1·89	1·89	1·91	1·91	7·44
$NHPr^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	24·3	1·90	1·90	1·91	1·92	7·24
$NHBu^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	23·8	1·85	1·84	1·85	1·84	7·20
$NHAm^n{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	20·9	1·85	1·84	1·85	1·86	7·03
$n\text{-}C_6H_{13}{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CN$	21·5	1·83	1·84	1·85	1·84	7·04
Mean (N–H)	23·2	1·86	1·86	1·87	1·87	7·19

The (N–O) constants were deduced from the data on alkyl nitrates, $R{\cdot}CH_2{\cdot}O{\cdot}NO_2$, and aliphatic nitro-compounds $R{\cdot}CH_2{\cdot}NO_2$ (Part XXIII, *J.*, 1948, 1833): the constants $(C–O)_{acetals}$ (Table 14) and (C–N) (Table 36) were used in the calculations. The resulting (N–O) constants and $(C–O)_{acetals}$ were used in the evaluation of the (N=O) constants from alkyl nitrites $R{\cdot}O{\cdot}N{:}O$ (Part XXIII, *loc. cit.*). Tables 40 and 41 give the various values obtained.

TABLE 40. *Values for* (N–O) *from alkyl nitrates and nitroparaffins.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$EtNO_3$	13·4	2·35	2·37	2·40	2·45	18·56
Pr^nNO_3	13·4	2·51	2·50	2·56	2·55	18·89
Bu^nNO_3	15·5	2·42	2·46	2·46	2·50	19·00
Mean (N–O)	14·1	2·42	2·43	2·49	2·51	18·82

TABLE 41. *Values for* (N=O) *from alkyl nitrites.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
Bu^nNO_2	52·5	4·00	4·04	4·11	4·21	32·16
Am^nNO_2	51·8	3·91	3·95	4·01	4·12	32·29
n-C_6H_{13}·NO_2	52·2	3·97	4·00	4·08	4·18	32·33
Mean (N=O)	52·2	3·96	4·00	4·07	4·17	32·26

The (N=O) constants were employed to compute those for (N→O) from the data for nitroparaffins, RN(→O):O (Table 42). An independent determination is possible from alkyl nitrates RO·N(→O):O, and alkyl nitrites RO·N:O; the figures for R = Bu^n (Part XXIII, *loc. cit.*), the only experimental observations available at present, are :

(*P*) 17·2, (R_C) 1·76, (R_D) 1·77, (R_F) 1·77, ($R_{G'}$) 1·76, and (Mn_D^{20}) 25·56.

TABLE 42. *Values for* (N→O) *from nitroparaffins.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$MeNO_2$	20·7	1·79	1·79	1·81	1·81	25·08
$EtNO_2$	19·1	1·80	1·80	1·82	1·80	25·43
Pr^nNO_2	17·4	1·74	1·75	1·75	1·78	25·27
Pr^iNO_2	19·3	1·71	1·69	1·71	1·69	24·94
Bu^nNO_2	16·1	1·83	1·82	1·84	1·81	25·61
Am^nNO_2	15·5	1·80	1·79	1·81	1·78	25·26
n-C_6H_{13}·NO_2	15·1	1·82	1·81	1·84	1·82	25·29
Mean (N→O)	17·6	1·78	1·78	1·80	1·78	25·27

The observations on aliphatic ketoxime *O*-alkyl ethers CRR′:NOR″ were employed to evaluate the (C=N) constants with the aid of the values of (C–C), $(C–O)_{ethers}$, and (N–O) (Table 43). These are slightly higher than the (C=N) constants deduced from aliphatic aldoximes CHR:N·OH [$(O–H)_{alcohols}$ being used : Table 44] and aliphatic ketoximes CRR′:N·OH (Table 45).

TABLE 43. *Values for* (C=N) *from aliphatic ketoxime O-alkyl ethers.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
CMe_2:N·OMe	33·5	3·65	3·72	3·78	3·91	24·64
CMe_2:N·OEt	32·9	3·82	3·89	3·96	4·09	24·08
CMe_2:N·OPr^n	32·3	3·68	3·75	3·81	3·94	24·25
CMeEt:N·OEt	33·2	3·74	3·81	3·88	4·00	24·01
CMeEt:N·OPr^n	27·8	3·51	3·58	3·64	3·76	24·25
CEt_2:N·OEt	28·3	3·64	3·71	3·78	3·90	24·14
CEt_2:N·OPr^n	28·2	3·57	3·62	3·70	3·83	24·23
CMePr^n:N·OEt	29·4	3·77	3·83	3·89	4·03	24·18
CMePr^n:N·OPr^n	28·8	3·63	3·67	3·74	3·89	24·21
CEtPr^n:N·OEt	28·8	3·78	3·82	3·91	4·03	24·09
CEtPr^n:N·OPr^n	28·0	3·69	3·73	3·83	3·94	24·15
CPr^n_2:N·OEt	27·3	3·76	3·80	3·89	3·98	24·10
CPr^n_2:N·OPr^n	26·3	3·77	3·79	3·88	4·01	23·29
Mean (C=N)	29·6	3·69	3·76	3·82	3·95	24·13

TABLE 44. *Values for* (C=N) *from aliphatic aldoximes.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
CHMe:N·OH	36·0	3·63	3·64	3·72	3·81	24·36
CHEt:N·OH	34·0	3·58	3·63	3·70	3·80	24·06
CHPr^n:N·OH	33·2	3·62	3·67	3·74	3·85	24·15
Mean $(C=N)_{aldoximes}$	34·4	3·61	3·65	3·72	3·82	24·19

TABLE 45. *Values for* (C=N) *from aliphatic ketoximes.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$CMeEt{:}N{\cdot}OH$	31·1	3·63	3·68	3·75	3·85	24·54
$CEt_2{:}N{\cdot}OH$	28·4	3·55	3·62	3·67	3·78	24·54
$CMePr^n{:}N{\cdot}OH$	29·3	3·61	3·67	3·74	3·84	24·50
$CEtPr^n{:}N{\cdot}OH$	27·3	3·45	3·53	3·57	3·68	24·35
$CPr^n_2{:}N{\cdot}OH$	24·1	3·44	3·49	3·55	3·67	24·19
Mean $(C{=}N)_{ketoximes}$	28·0	3·54	3·60	3·66	3·76	24·42

The most accurate values for (N–N) were obtained from the data on *NN*-dialkylhydrazines, $NR_2{\cdot}NH_2$, and secondary amines, NHR_2:

$$(N{-}N) = NR_2{\cdot}NH_2 - NHR_2 - (N{-}H)$$

Another procedure, from dialkyl nitrosamines, utilises the previously determined values for (N=O) (Table 41):

$$(N{-}N) = NR_2{\cdot}NO - NR_2 + (N{-}H) - (N{=}O)$$

Both series of results are given in Table 46: the divergences for (*P*) and (Mn_D^{20}) are noteworthy.

TABLE 46. *Values for* (N–N) *from* NN-*dialkylhydrazines.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$NEt_2{\cdot}NH_2$	6·7	1·91	1·95	1·98	2·02	16·65
$NPr^n_2{\cdot}NH_2$	6·8	1·97	2·02	2·05	2·10	18·16
$NBu^n_2{\cdot}NH_2$	5·6	1·93	1·96	2·01	2·03	16·43
$NAm^n_2{\cdot}NH_2$	5·8	1·99	2·01	2·05	2·11	16·99
Mean (N–N)	6·2	1·95	1·99	2·02	2·08	16·81
Values for (N–N) *from dialkylnitrosamines*						
$NEt_2{\cdot}NO$	7·2	1·87	1·89	2·03	2·12	20·47
$NPr^n_2{\cdot}NO$	6·6	1·94	1·98	2·12	2·22	20·79
$NBu^n_2{\cdot}NO$	2·4	1·89	1·92	2·08	2·13	20·83
$NAm^n_2{\cdot}NO$	0	1·95	1·97	2·11	2·24	20·88
$(n\text{-}C_6H_{13})_2N{\cdot}NO$	−2·4	2·04	2·05	2·22	2·33	20·61
Mean (N–N)	?	1·94	1·96	2·11	2·21	20·72

The constants for the N=N bond, recorded in Table 47, were deduced from the observations on dialkyl azodiformates, $RO_2C{\cdot}N{:}N{\cdot}CO_2R$, and dialkyl oxalates, $RO_2C{\cdot}CO_2R$ (Part XIII, *J.*, 1948, 639): $(N{=}N) = RO_2C{\cdot}N{:}N{\cdot}CO_2R - RO_2C{\cdot}CO_2R - 2(C{-}N) + (C{-}C)$.

TABLE 47. *Values for* (N=N) *from dialkyl azodiformates.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$EtO_2C{\cdot}N{:}N{\cdot}CO_2Et$	45·6	4·33	4·36	—	—	25·41
$Pr^nO_2C{\cdot}N{:}N{\cdot}CO_2Pr^n$	44·4	4·13	4·15	—	—	25·67
$Bu^nO_2C{\cdot}N{:}N{\cdot}CO_2Bu^n$	41·4	3·82	3·85	—	—	26·09
Mean (N=N)	44·8	4·09	4·12	—	—	25·72

Some experimental data on azohydrocarbons are given by Barrick, Drake, and Lochte (*J. Amer. Chem. Soc.*, 1936, **58**, 160). We have used their figures to calculate the constants for the N=N bond and have employed our own constants for the alkyl groups (Table 11) and for (C–N) (Table 26). The results are given below and, having regard to the instability of these aliphatic azohydrocarbons, the agreement with our own constants is moderately satisfactory.

	(*P*)	(R_C)	(R_D)	(R_F)
$Pr^iN{:}NPr^i$	42·2	4·22	4·31	4·32
$Bu^sN{:}NBu^s$	44·7	4·76	4·78	4·88

The constants for the C=S bond were determined from the data on alkyl xanthates $CS(OR){\cdot}SR'$ (Part XXIII, *J.*, 1948, 1840) by using the expression:

$$(C{=}S) = CS(OR){\cdot}SR' - 2(C{-}S) - 2(C{-}O)_{acetals} - (R) - (R')$$

The results are given in Table 48.

TABLE 48. *Values for* (C=S) *from dialkyl xanthates.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
CS(OEt)·SEt	73·6	11·41	11·62	12·19	12·72	64·88
CS(OPr^n)·SPr^n	70·9	11·75	11·95	12·56	13·13	65·17
CS(OEt)·SBu^n	71·0	11·75	11·97	12·58	13·14	65·09
CS(OBu^n)·SEt	71·1	11·74	11·96	12·57	—	65·09
CS(OBu^n)·SBu^n	68·0	11·83	12·06	12·68	13·21	64·87
Mean (C=S)	70·9	11·70	11·91	12·52	13·05	65·02

The literature data for carbon disulphide (see *J.*, 1948, 1841) give for (C=S) (*P*) 71·8, (R_C) 10·56, (R_D) 10·70, (R_F) 11·03, ($R_{G'}$) 11·32, and (Mn_D^{20}) 61·97.

TABLE 49. *Values for* (S–O) *from alkyl sulphates and alkyl sulphites.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
R = Me	36·2	4·77	4·81	4·90	4·98	36·23
R = Et	34·9	4·85	4·92	5·00	5·10	37·63
R = Pr^n	34·8	4·99	5·04	5·13	5·21	37·55
R = Bu^n	33·2	4·93	4·99	5·07	5·14	35·04
Mean (S–O)	34·8	4·88	4·94	5·03	5·11	37·13

TABLE 50. *Values for* (S→O) *from* $R_2SO_4 - R_2SO_3$.

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
R = Me	18·2	−0·07	−0·08	−0·15	−0·19	19·79
R = Et	18·8	−0·11	−0·14	−0·20	−0·26	19·37
R = Pr^n	16·8	−0·30	−0·33	−0·40	−0·46	20·80
R = Bu^n	17·4	−0·21	−0·25	−0·32	−0·36	23·40
Mean (S→O)	17·8	−0·17	−0·20	−0·27	−0·32	20·84

TABLE 51. *Bond parachors, bond refractions* (*at* 20°) *and bond-refraction coefficients* (*at* 20°).

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
(C–H)	17·85	1·669	1·676	1·693	1·704	3·87
(C–C)	4·30	1·286	1·296	1·301	1·328	12·86
(C=C)	28·5	4·12	4·17	4·28	4·38	9·39
(C≡C)$_{\text{terminal}}$	53·5	5·82	5·87	5·97	6·07	25·04
(C≡C)$_{\text{non-terminal}}$ *	—	—	6·24	—	—	24·83
(C–C)$_{\text{cyclopropane}}$	8·4	1·48	1·49	1·52	1·54	11·28
(C–C)$_{\text{cyclobutane}}$	6·8	1·36	1·37	1·38	1·41	11·44
(C–C)$_{\text{cyclopentane}}$	5·2	1·25	1·26	1·26	1·28	11·95
(C–C)$_{\text{cyclohexane}}$	4·5	1·26	1·27	1·28	1·30	12·24
(C_{ar}–C_{ar})	16·5	2·660	2·688	2·760	2·822	15·67
(C–F) *	28·2	1·45	1·44	1·44	1·45	28·27
(C–Cl)	57·4	6·48	6·51	6·58	6·64	56·80
(C–Br)	70·9	9·32	9·39	9·54	9·68	124·51
(C–I)	92·4	14·47	14·61	14·96	15·28	202·46
(C–O)$_{\text{ethers}}$	12·4	1·53	1·54	1·55	1·57	17·71
(C–O)$_{\text{acetals}}$	11·3	1·45	1·46	1·47	1·48	17·46
(C=O)	40·3	3·30	3·32	3·36	3·39	29·39
(C=O)$_{\text{methyl ketones}}$	42·6	3·46	3·49	3·53	3·57	29·50
(C–S)	26·6	4·57	4·61	4·70	4·78	32·84
(C=S)	70·9	11·70	11·91	12·52	13·05	65·02
(C–N)	6·4	1·55	1·57	1·59	1·63	14·51
(C=N)	29·3	3·69	3·76	3·82	3·95	24·13
(C≡N)	61·4	4·80	4·82	4·87	4·91	29·91
(O–H)$_{\text{alcohols}}$	20·3	1·65	1·66	1·67	1·68	13·15
(O–H)$_{\text{acids}}$	20·0	1·80	1·80	1·83	1·83	10·54
(S–H)	42·1	4·77	4·80	4·87	4·94	23·79
(S–S)	49·0	8·02	8·11	8·28	8·45	53·83
(S–O)	34·8	4·88	4·94	5·03	5·11	37·13
(S→O)	17·8	−0·17	−0·20	−0·27	−0·32	20·84
(N–H)	19·9	1·76	1·76	1·79	1·80	7·26
(N–O)	14·1	2·42	2·43	2·49	2·51	18·82
(N→O)	17·6	1·78	1·78	1·80	1·78	25·27
(N=O)	52·2	3·96	4·00	4·07	4·17	32·26
(N–N)	6·2	1·95	1·99	2·02	2·08	16·81
(N=N)	44·8	4·09	4·12	—	—	25·72

* Preliminary values.

The experimental data for alkyl sulphates and sulphites (Part VII, *J.*, 1943, 16; Part XXIII, *J.*, 1948, 1836) may be employed to calculate the constants of the S–O bond:

$$2(S{-}O) = 2(RO)_2SO - (RO)_2SO_2 - 2(R) - 2(C{-}O)_{acetals}$$

The results are collected in Table 49. The constants for the S→O bond (Table 50) (strictly speaking, this is the bond in which oxygen is attached only to sulphur) are obtained directly from alkyl sulphates and alkyl sulphites:

$$(S{\rightarrow}O) = R_2SO_4 - R_2SO_3$$

The bond parachors, bond refractions for the C, D, F, and G′ lines at 20°, and the bond-refraction coefficients 20° so far deduced are summarised in Table 51.

The bond constants (C_{ar}–C_{ar}) were determined from our own measurements of d_4^{20} and the refractive indices of pure benzene: the parachor (206·23) was computed from Sugden's figures for the surface tension at various temperatures (*J.*, 1924, **125**, 31) and the relation for the variation of density with temperature given in "International Critical Tables." The values obtained, our own values being used for (C–H), are: (P) 16·52, (R_C) 2·660, (R_D) 2·688, (R_F) 2·760, ($R_{G'}$) 2·822, and (Mn_D^{20}) 15·67.

A large number of monosubstituted benzenes have been studied in the present series, and an attempt has been made to investigate the character of the bond between the aromatic ring and the substituent element or group (C_{ar}–X) with the aid of the bond refractions for the D line. Table 52 gives the ratios of the bond refractions (D line) for the single and the double bonds so far investigated.

TABLE 52. *Single : double bond ratios for bond refractions* (D *line*).

Elements in bond	Bond refraction: single	Bond refraction: double	Ratio
Carbon–carbon	1·296	4·17	1 : 3·2
Carbon–oxygen	1·54 (ethers)	3·32	1 : 2·2
	1·46 (acetals)	3·32	1 : 2·3
Carbon–nitrogen	1·57	3·75	1 : 2·4
Carbon–sulphur	4·61	11·91	1 : 2·6
Nitrogen–oxygen	2·43	4·00	1 : 1·65
Nitrogen–nitrogen	1·99	4·12	1 : 2·1
		Mean	1 : 2.3

The ratio 1 : 2·3 is employed for computing the refractions of double bonds which have not yet been investigated or cannot be determined by the usual methods, *e.g.*, (C=Cl) from (C–Cl), etc. This is, of course, only a rough approximation and it may well be that the derived figures, *e.g.*, for Ph–X where X is halogen, are too low. The results of the calculations of the bond refractions (for the D line) and the percentage double-bond character p_d of the (C_{ar}–X) link are collected in Table 53; (C_6H_5) was computed from C_6H_6 – (C–H): p_d was obtained from the expression

$$p_d = 100\ (r_{obs} - r_{single})/(r_{double} - r_{single})$$

where r_{single} and r_{double} are the bond refractions of the single- and double-bond links, respectively (cf. Cresswell, Jeffery, Leicester, and Vogel, *Research*, 1949, **2**, 46). The alkyl cinnamates (Part XVI, *J.*, 1948, 661) and phenylpropiolates (Part XVII, *J.*, 1948, 676) contain conjugated systems and are therefore too complex to be investigated by this simple procedure.

It is of interest to investigate the bond constants when two or more halogens are attached to the same carbon atom. The values for 2(C–Cl) were computed from the experimental data (Part XXIII, *J.*, 1948, 1834) for alkyl dichloroacetates and alkyl succinates, the known values for (C–C) and (C–H) being used. The results are collected in

TABLE 53. *Bond refractions and the percentage double-bond character of links between* X *and the aromatic ring in* C_6H_5X.

	R_D	bond	$(C_{ar}–X)$	p_d
PhMe	31·10	(C_{ar}–C)	1·59	10
PhEt	35·75	,,	1·59	10
PhPr^n	40·43	,,	1·60	10·5
PhBu^n	45·08	,,	1·63	11·5
PhAm^n	49·73	,,	1·62	11
n-C_6H_{13}·Ph	54·29	,,	1·57	10
PhCOMe	36·27	(C_{ar}–COR)	1·97	23
PhCOEt	40·83	,,	2·06	26
PhCOPr^n	49·62	,,	2·16	30
$PhCH_2$·COMe	40·48	(C_{ar}–CH_2·COR)	1·54	8
$PhCH_2$·COEt	44·99	,,	1·58	10
$PhCH_2$·COPr^n	49·62	,,	1·47	6
$PhCH_2$·CH_2·COMe	45·07	(C_{ar}–CH_2·CH_2·COR)	1·57	9
$PhCH_2$·CH_2·COEt	49·58	,,	1·54	8
$PhCH_2$·CH_2·COPr^n	54·20	,,	1·41	4
$PhCO_2$Et	42·57	(C_{ar}–CO_2R)	1·93	22
$PhCO_2$Pr^n	47·22	,,	1·88	20
$PhCO_2$Bu^n	51·90	,,	1·94	22
$PhCH_2$·CO_2Me	41·84	(C_{ar}–CH_2·CO_2R)	1·49	7
$PhCH_2$·CO_2Et	46·55	,,	1·54	8
$PhCH_2$·CO_2Pr^n	51·22	,,	1·54	8
$PhCH_2$·CO_2Bu^n	55·89	,,	1·59	9
$PhCH_2$·CH_2·CO_2Me	46·52	(C_{ar}–CH_2·CH_2·CO_2R)	1·57	9
$PhCH_2$·CH_2·CO_2Et	51·14	,,	1·51	8
$PhCH_2$·CH_2·CO_2Pr^n	55·81	,,	1·54	8
$PhCH_2$·CH_2·CO_2Bu^n	60·48	,,	1·58	10
PhOMe	32·88	(C_{ar}–OR)	1·83	16
PhOEt	37·70	,,	1·94	23
PhOPr^n	42·28	,,	1·93	22
PhOPr^i	42·39	,,	1·93	22
PhOBu^n	47·06	,,	2·11	32
PhOAm^n	51·64	,,	2·05	31
n-C_6H_{13}·OPh	56·38	,,	2·13	33
$PhCH_2$·OH	32·47	(C_{ar}–CH_2·OH)	1·42	4
$PhCH_2$·CH_2·OH	37·12	(C_{ar}–CH_2·CH_2·OH)	1·39	3
PhF	25·98	(C_{ar}–F)	1·48	2
PhCl	31·14	(C_{ar}–Cl)	6·64	2
CH_2Cl	36·03	(C_{ar}–CH_2Cl)	1·66	12
PhBr	33·99	(C_{ar}–Br)	9·49	1
$PhCH_2$·CH_2Br	43·81	(C_{ar}–CH_2·CH_2·Br)	1·98	21
PhI	39·15	(C_{ar}–I)	14·61	0·2
$PhCH_2$·CH_2I	48·78	(C_{ar}–CH_2·CH_2I)	1·72	15
PhCN	31·58	(C_{ar}–CN)	2·26	33
$PhCH_2$·CN	35·22	(C_{ar}–CH_2·CN)	1·30	0
$PhNO_2$	32·72	(C_{ar}–NO_2)	2·44	40
$PhNH_2$	30·56	(C_{ar}–NH_2)	2·54	44
$PhCH_2$·NH_2	34·45	(C_{ar}–CH_2·NH_2)	1·50	7
PhNHMe	35·67	(C_{ar}–NHR)	2·83	58
PhNHEt	40·45	,,	2·96	64
PhNHPr^n	44·72	,,	2·96	64
PhNHBu^n	49·80	,,	3·10	70
$PhNMe_2$	40·81	(C_{ar}–NR_2)	3·16	73
$PhNEt_2$	50·20	,,	3·15	72
$PhNPr^n_2$	59·56	,,	3·30	79
$PhNBu^n_2$	68·84	,,	3·27	78
PhSH	34·52	(C_{ar}–SH)	5·22	8
SPh_2	59·77	(C_{ar}–SPh)	5·38	11
PhSMe	39·42	(C_{ar}–SR)	5·35	10
PhSEt	44·19	,,	5·42	11
PhSPr^n	48·85	,,	5·45	11
PhSPr^i	48·98	,,	5·42	11
PhSBu^n	53·59	,,	5·56	13
PhSAm^n	58·23	,,	5·36	10
n-C_6H_{13}·SPh	62·96	,,	5·59	13

Table 54; those for methylene chloride, ethylidene dichloride, and acetylene tetrachloride are also included, but are less trustworthy owing to the difficulty of preparing and storing these polyhalogenated hydrocarbons in a state of purity.

TABLE 54. *Values for* 2(C–Cl) *from compounds containing the* $-CCl_2$ *Group.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$CHCl_2 \cdot CO_2Me$	111·3	13·27	13·35	13·50	13·63	112·82
$CHCl_2 \cdot CO_2Et$	113·7	13·26	13·34	13·49	13·62	112·47
$CHCl_2 \cdot CO_2Pr^n$	111·6	13·28	13·35	13·51	13·63	112·43
$CHCl_2 \cdot CO_2Bu^n$	110·3	13·20	13·28	13·42	13·56	112·58
Mean 2(C–Cl)	111·7	13·25	13·33	13·48	13·61	112·58
CH_2Cl_2	111·8	12·96	13·03	13·19	13·31	113·06
$CH_3 \cdot CHCl_2$	112·2	13·04	13·12	13·26	13·40	111·72
$CHCl_2 \cdot CHCl_2$	108·9	12·92	12·98	13·19	13·25	115·15
Mean (C–Cl) from monohalogeno-compounds	57·4	6·48	6·51	6·58	6·64	56·80

The bond constants for 3(C–Cl) were similarly determined from the experimental data (Part XXIII, *loc. cit.*) for alkyl trichloroacetates and alkyl succinates. These, as well as those for the comparatively unstable chloroform and methylchloroform, are presented in Table 55.

TABLE 55. *Values for* 3(C–Cl) *from compounds containing the* CCl_3 *group.*

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
$CCl_3 \cdot CO_2Me$	163·3	19·87	19·98	20·22	20·40	168·97
$CCl_3 \cdot CO_2Et$	166·0	20·03	20·14	20·37	20·56	168·13
$CCl_3 \cdot CO_2Pr^n$	165·2	19·87	19·98	20·22	20·39	168·13
$CCl_3 \cdot CO_2Bu^n$	164·6	19·89	20·01	20·23	20·44	168·22
Mean 3(C–Cl)	164·8	19·91	20·03	20·26	20·45	168·36
$CHCl_3$	165·3	19·59	19·69	19·94	20·12	168·79
$CH_3 \cdot CCl_3$	171·4	21·07	21·20	21·44	21·65	180·20

The bond constants for (C–Cl) in carbon tetrachloride are: (*P*) 55·3, (R_C) 6·58, (R_D) 6·61, (R_F) 7·72, ($R_{G'}$) 6·77, and (Mn_D^{20}) 56·16.

The few polybromo-compounds so far investigated give the following results:

	(*P*)	(R_C)	(R_D)	(R_F)	($R_{G'}$)	(Mn_D^{20})
2(C–Br) from CH_2Br_2	139·3	18·42	18·54	18·87	19·13	260·21
2(C–Br) from $CHBr_2 \cdot CHBr_2$	—	18·54	18·67	18·99	—	272·37
3(C–Br) from $CHBr_3$	209·9	27·98	28·18	28·69	29·09	409·96
Mean (C–Br) from monobromo-compounds	70·9	9·32	9·39	9·54	9·68	124·51

It is difficult to draw any trustworthy conclusions from these few results, particularly from bromoform which is known to be unstable when pure.

The Structures of The Esters of Oxy-acids and of Related Compounds.—In Part XXIII (*J.*, 1948, 1841) the structures of the nitro-group, alkyl nitrates, thionyl chloride, sulphuryl chloride, alkyl sulphites, alkyl sulphates, phosphorus oxychloride, and trialkyl orthophosphates were considered from the view-point of atomic and structural parachors and refractions, and it was suggested that the results indicate the presence of co-ordinate links in these compounds. It seems appropriate to consider the subject again by using the bond constants. Particular attention will be paid to the values of the bond refractions, since these are the most sensitive to changes of structure; the results for bond parachors and bond-refraction coefficients will, however, be included for completeness.

The presence of a co-ordinate link in nitro-compounds and alkyl nitrates seems to be generally accepted. The bond constants deduced above for the various nitrogen–oxygen links are:

	(*P*)	(R_D)	(Mn_D^{20})
(N–O)	14·1	2·43	18·82
(N→O)	17·6	1·78	25·27
(N=O)	52·2	4·00	32·26

It will be noted that the refraction of the N→O link is less than that of the normal covalent bond N–O and very much less than that of the double bond N=O.

The constants for the two types of bonds in alkyl sulphites and alkyl sulphates, represented as (S–O) and (S→O) are:

	(*P*)	(R_D)	(Mn_D^{20})		(*P*)	(R_D)	(Mn_D^{20})
(S–O)	34·8	4·94	37·13	(S→O)	17·8	−0·20	17·80

The refraction is very much less for the S→O link, but no explanation can at present be offered for the negative value: the parachor differences between the two links are particularly noteworthy. It will be recalled that in the deduction of the constants for the S–O link (Table 49), it was assumed that the link between sulphur and oxygen only in alkyl sulphites was identical with the two such links in alkyl sulphates: a rigid proof of the validity of this assumption is desirable. New measurements are in progress on compounds containing the S–O link only (*e.g.*, RO·S·S·OR) and further discussion must be postponed until these have been completed. The following facts, however, do not support the presence of the S=O link, as has recently been postulated (see below):

(i) R_D for SO_2Cl_2 is 21·43 and for $SOCl_2$ 22·12: the molecular refractions of the alkyl sulphates are slightly *less* than those of the alkyl sulphites (Part XXIII, *J.*, 1948, 1835).

(ii) By subtracting R_D for the alkyl sulphides (Part VII, *J.*, 1943, 16) from R_{He} for the alkyl sulphoxides (Strecker and Spitaler, *Ber.*, 1926, **59**, 1755), the refractions for the sulphur to oxygen link are obtained; they are 0·90, 0·71, and 0·73 for R = Me, Et, and Pr^n, severally. New experiments on sulphoxides are in progress in order to determine the constants with greater accuracy.

(iii) Strecker and Spitaler (*loc. cit.*) have determined R_{He} for dimethyl, diethyl, and di-*n*-propyl sulphones at 50—100° and find R_{He} to be substantially the same as for the corresponding sulphoxides. The molecular refractions at 25° for allyl phenyl sulphide, sulphoxide, and sulphone are 48·46, 49·13, and 48·72, respectively; for crotyl phenyl sulphide and sulphone 53·50 and 53·34, respectively; and for *sec.*-butyl phenyl sulphide and sulphone, 53·36 and 53·63, respectively (Cope, Morrison, and Field, *J. Amer. Chem. Soc.*, 1951, **72**, 64). Experiments on liquid sulphones are in progress in order to confirm these highly significant results.

Note. The constants given for sulphones in *J.*, 1948, 1845 refer to the $C–SO_2–C$ results and *not* to the O_2 grouping: they were obtained from $R_2SO_2 - R_2$.

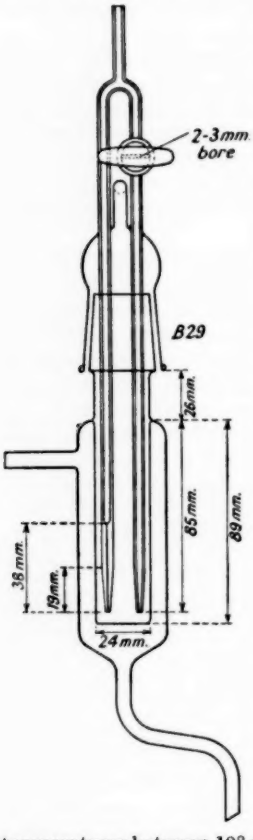
The observations on trialkyl orthophosphates (Part VII, *J.*, 1943, 17) do not support the view that the phosphorus to oxygen link is a double bond. Jones, Davies, and Dyke's data (*J. Phys. Chem.*, 1933, **37**, 583) for triethyl, tri-*iso*-butyl, and tri-*n*-amyl phosphites lead to the following values for the P–O link for the D-line: 3·22, 3·22, and 3·13, or a mean of 3·19. The less accurate experimental figures on cyclic phosphorus compounds given by Lucas, Mitchell, and Scully (*J. Amer. Chem. Soc.*, 1951, **72**, 5491) when combined with our own results for phosphorus trichloride (Part XXIII, *loc. cit.*) give a mean value of 3·00 for the (P–O) link. The bond refractions for the (P→O) link in trialkyl orthophosphates, computed with (P–O) 3·19 and $(C–O)_{acetals}$ are: R = Me, −1·21; R = Et, −1·13; R = Pr^n, −1·25; R = Pr^i, −1·15; R = Bu^n, −1·20; R = Bu^i and R = Am^n, −1·51. The mean value is −1·26. The figure obtained directly from $POCl_3 - PCl_3$ (*J.*, 1948, 1835) is −1·22.

The general conclusion may be drawn that bond-refraction data do not support the view that alkyl sulphites, alkyl sulphates, alkyl orthophosphates, and related compounds, and sulphoxides and sulphones, contain double bonds. The detailed arguments, based on many approximations, put forward by Phillips, Hunter, and Sutton (*J.*, 1945, 146) in support of the double-bond theory have been adversely criticised by Wells (*J.*, 1949, 55); in particular, he has shown that the abnormal shortness of many bond lengths cannot at present be explained satisfactorily. The authors feel that a knowledge of the physical constants of unequivocal examples of single bonds (S–O), (P–O), etc., or of double bonds (S=O), etc., would materially assist the solution of the problem. Infra-red studies appear to have led to different results in deciding between various alternative structures. Barnard, Fabian, and Koch (*J.*, 1949, 2442) conclude from infra-red studies of selected sulphoxides and sulphones that "it is unambiguously demonstrated that the sulphur–oxygen link is nearly a covalent double bond and contains a minor proportion of the polar co-ordinate single-bond structure which is relatively more important in the sulphoxides than in the sulphones." Koch and Moffitt (*Trans. Faraday Soc.*, 1951, **47**, 8) conclude "that the double-bonded structure of the S–O linkages in sulphones is no longer in doubt." On the other hand infra-red spectrum studies by Amstutz, Hundsberger, and Chessick (*J. Amer. Chem. Soc.*, 1951, **73**, 1220) lead to the conclusions "that in sulphoxides the bond between

sulphur and oxygen has considerable double-bond character with possible minor contributions from a semi-ionic structure, $-\overset{\oplus}{S}-\overset{\ominus}{O}$; and that sulphones are a resonance hybrid of the two forms $R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\downarrow}}{S}}-R$ and $R-\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\|}}{S}}-R$."

Experimental

Physical Measurements.—Surface tensions were usually measured by the capillary-rise method (Part VII, *J.*, **1943**, 18); the constant K of the apparatus used was 2·3282. Densities were determined with a " Phœnix " or " Pyrex " glass pycnometer (Part III, *J.*, **1938**, 1325; Part VII, *loc. cit.*). In the tabulated results t is the temperature, $H = h - 0{\cdot}24$, where h is the observed difference in height (in mm.) in the two arms of the U-tube, d_4^t the density at $t°$ (calculated from the observed densities by assuming a linear variation with temperature), γ the surface tension (dynes/cm.) computed from the equation $\gamma = Khd$, and P is the parachor.



For those liquids which did not appear to wet glass and for those cases where an independent check was required, the maximum bubble pressure method (compare Sugden, *J.*, 1922, **121**, 864; 1924, **125**, 28) was employed. The apparatus, shown in the figure, is an improved version of that described by Sugden (*loc. cit.*). It was constructed of " Pyrex " or " Hysil " glass; the standard ground-glass joint (B29) was external; the tubes comprising the actual bubbler were entirely of precision bore (" Hysil Veridia," 2—3 mm. in diameter), the narrow precision bore capillary (0·1—0·2 mm. in diameter and *ca.* 4 cm. long) being sealed to that of the wider bore; both capillaries were ground externally to conical form. (The wider capillary is shown of conical bore in the figure for the sake of clarity, but was in fact of uniform bore throughout.) The outer vessel of the bubbler was surrounded by a sealed-on glass jacket through which suitable vapours (redistilled methylene chloride, chloroform, trichloroethylene, etc.) could be passed for measurements at various temperatures; the temperature was read on a standardised Anschütz-type thermometer (with sealed-in glass scale) dipping directly in the liquid. The gauge consisted of a water-jacketed U-tube (40 cm. long and 4 mm. bore) filled with absolute alcohol tinted with a little magenta; the liquid levels were viewed against an illuminated glass screen placed at a distance of 2—3 cm. in order to eliminate heating effects; a thermometer was immersed in the water jacket. The difference in heights in the two arms of the U-tube was determined by means of a Pye " universal reading cathetometer," fitted with a vernier reading to 0·05 mm.: suitable precautions were taken that both the U-tube and the cross-wire in the eyepiece of the telescope objective were vertical. The mercury aspirator was similar to that described by Sugden (*loc. cit.*). The density of the tinted alcohol was determined at several temperatures between 10° and 30°, and a graph was drawn relating temperature and (density × g) (g = 981 cm./sec.²). The difference between the pressures required to liberate bubbles from the two tubes, Δp (dynes/cm.²), was obtained from the expression:

Δp = difference in pressure on gauge (cm. of alcohol) × {density of alcohol at temperature of gauge × g}

The correction factor ϕ was computed from the equation:

$$\phi = 1 + 0{\cdot}69r_{25}gd_4^t/\Delta p$$

where r_2 is the radius of the wide tube in cm. (0·126 cm.) and d_4^t is the density of the liquid at the temperature of observation. The constant of the apparatus A was deduced from the expression $\gamma = A\phi\Delta p$, pure benzene being used, γ being the surface tension. The surface tensions of benzene at various temperatures were those determined by Sugden (*J.*, 1924, **125**, 31; "The Parachor and Valency," 1930, p. 211). The value of A found in this manner was 0·005393. In the tabulated results, the above symbols are used with the addition of the parachor P calculated in the usual manner: allowance was made for the density of the vapour (computed as described by Sugden, Reed, and Wilkins, *J.*, 1925, **127**, 1540) when the temperature of measurement was within 60° of the b. p. of the sample.

Most of the refractive-index measurements were made at 20° ± 0·02° in a Zeiss Pulfrich refractometer. Some determinations (including those on benzene) were made with a Hilger–Chance refractometer, precision model, for liquids. The results with the two instruments agreed to within 0·0001 for the C, D, and F lines, but differences as high as 0·0004 were sometimes found for the G′ line. Where 20° is used, 20·0° is to be understood; n_C, n_D, n_F, and n_G are to be taken as referring to $n_C^{20\cdot0}$, etc., and R_C, etc., to $[R_L]_C$, etc.

Unless otherwise stated, all b. p.s are corrected. All the compounds were distilled immediately before the measurements were made. Analyses are by Drs. Weiler and Strauss. The numbering of compound in Clarendon type follows from Part XXIII (*J.*, 1948, 1855). References to compounds, the preparation of which is described in previous Parts of this series, will be abbreviated, *e.g.*, XXIII, **605**.

Preparation of pure compounds

Aliphatic Aldoximes and Ketoximes.—Acetaldoxime. This was prepared from redistilled acetaldehyde (b. p. 22·5°), hydroxylamine hydrochloride and sodium carbonate solution. The dried product was distilled in an all-glass apparatus through a Widmer column: a middle fraction, b. p. 115·2°/766 mm., was collected for the physical measurements.

Propaldoxime. This was prepared from freshly distilled propaldehyde (B.D.H.) (b. p. 49—49·5°); b. p. 134°/761 mm.

n-*Butaldoxime.* Pure butaldehyde was obtained by drying the commercial product (anhydrous magnesium sulphate) and distilling it through a Widmer column; it had b. p. 73°/755 mm. This was converted into the oxime, b. p. 151°/750 mm., in the usual manner.

Diethyl ketoxime. This was prepared by the method described in *Org. Synth.*, 1931, **11**, 54 for *n*-heptaldoxime (on $\frac{1}{10}$th scale); 33 g. of diethyl ketoxime, b. p. 165—166°/763 mm., were obtained from 34·4 g. of diethyl ketone. Redistillation gave the pure compound, b. p. 165·5°/765 mm.

Similarly prepared were: ethyl methyl ketoxime (28 g. from 28·8 g. of ketone), b. p. 151·5°/770 mm.; methyl *n*-propyl ketoxime (27 g. from 34·8 g. of ketone), b. p. 168°/754 mm.; ethyl *n*-propyl ketoxime (27 g. from 40 g. of ketone), b. p. 180°/753 mm.; and di-*n*-propyl ketoxime (26·5 g. from 45·6 g. of ketone), b. p. 194·5—195°/755 mm.

Ketoxime O-*Alkyl Ethers.—General.* Only the *O*-methyl ether of acetoxime can be prepared by methylation with methyl sulphate and alkali since acetone, formed as a by-product by the hydrolysis of the ketoxime, can be readily removed by washing with water. With higher ketoximes the ketone is not easily separated by fractionation without considerable sacrifice of yield. The *O*-ethyl ethers of ketoximes were readily prepared by ethylation with ethyl sulphate and alkali (compare Ponzio and Charrier, *Gazzetta*, 1907, **37**, 506); the *O*-*n*-propyl ethers were obtained by treatment in methanol solution with sodium methoxide and *n*-propyl iodide (compare Dunstan and Goulding, *J.*, 1906, **79**, 628).

Acetoxime O-*methyl ether.* Acetoxime (100 g.) was dissolved in a solution of sodium hydroxide (220 g.) in water (730 ml.), and methyl sulphate (252 g.) was added with stirring during 40 minutes with occasional water cooling; stirring was continued for a further 30 minutes, and the upper layer was separated, dried (anhydrous $MgSO_4$), and fractionated through a 10″ vacuum-jacketed Widmer column. The yield of acetoxime *O*-methyl ether, b. p. 72—73°/760 mm., was 40 g.; on redistillation, it boiled mostly at 73°/760 mm.

Acetoxime O-*ethyl ether.* Prepared as for the methyl ether, but at 60—70°, acetoxime *O*-ethyl ether (34 g. from 50 g. of acetoxime) was collected at 91—93°; on redistillation, it boiled largely at 93°/760 mm.

Similarly prepared were: *ethyl methyl ketoxime* O-*ethyl ether* (36 g. from 60 g. of ketoxime), b. p. 113°/761 mm. (Found: C, 63·0; H, 11·6; N, 11·9. $C_6H_{13}ON$ requires C, 62·6; H, 11·4; N, 12·2%); *diethyl ketoxime* O-*ethyl ether* (20 g. from 30 g. of ketoxime), b. p. 132·5°/764 mm. (Found: C, 65·3; H, 11·7; N, 11·1. $C_7H_{15}ON$ requires C, 65·0; H, 11·6; N, 10·8%); *methyl*

n-*propyl ketoxime* O-*ethyl ether* (32 g. from 50·5 g. of ketoxime), b. p. 134°/754 mm. (Found: C, 65·2; H, 11·8; N, 10·5%); and *ethyl* n-*propyl ketoxime* O-*ethyl ether* (32 g. from 57·5 g. of ketoxime), b. p. 152°/770 mm. (Found: C, 67·5; H, 12·2. $C_8H_{17}ON$ requires C, 67·1; H, 11·9%).

Acetoxime O-n-*propyl ether*. To a solution of sodium methoxide [from sodium (23 g.) in absolute methanol (300 ml.)] acetoxime (73 g.) dissolved in absolute methanol (100 ml.) was added, followed by *n*-propyl iodide (171 g.). The mixture became hot, and was kept for 2 days at the laboratory temperature, and then refluxed for 3 hours. About two-thirds of the methanol was distilled off, and excess of water was added to the distillate; the ethereal layer was separated, dried, and fractionated through a lagged Widmer or Dufton column. The yield of acetoxime *O-n*-propyl ether, b. p. 114—116°/747 mm., was 33 g.; on redistillation, most boiled at 116°/750 mm.

Similarly prepared were: *ethyl methyl ketoxime* O-n-*propyl ether* (34 g. from 80 g. of ketoxime), b. p. 136°/756 mm. (Found: C, 65·4; H, 11·6; N, 10·4%); *diethyl ketoxime* O-n-*propyl ether*, b. p. 153·5—154°/766 mm. (Found: C, 66·7; H, 12·0; N, 10·2%); *methyl* n-*propyl ketoxime* O-n-*propyl ether* (70 g. from 132 g. of ketoxime), b. p. 154°/755 mm. (Found: C, 67·4; H, 11·8%); *ethyl* n-*propyl ketoxime* O-n-*propyl ether* (28 g. from 140 g. of ketoxime), b. p. 170·5°/765 mm. (Found: C, 68·4; H, 12·2. $C_9H_{19}ON$ requires C, 68·7; H, 12·2%); and *di*-n-*propyl ketoxime* O-n-*propyl ether* (17 g. from 144 g. of ketoxime), b. p. 187°/749 mm. (Found: C, 69·8; H, 12·5. $C_{10}H_{21}ON$ requires C, 70·1; H, 12·3%).

NN-*Dialkylhydrazines*.—NN-*Diethylhydrazine*. (i) The following modification of Fischer's method (*Annalen*, 1879, **199**, 287) was employed. Diethylnitrosamine (XXIII, **574**) (102 g.), zinc dust (95%; 255 g.), and water (900 ml.) were stirred mechanically and the temperature was maintained at 25—30° whilst 85% acetic acid (370 ml.) was added during 2 hours. Stirring was continued, and the mixture was heated to and kept at 60° for 1 hour and then filtered hot. Next morning the zinc acetate crystals were filtered off and 50% sodium hydroxide solution was added to the filtrate at such a rate that a precipitate was just visible and steam distillation was continued until the distillate was no longer basic to litmus. The distillate was neutralised with concentrated hydrochloric acid (85 ml.) and a further 5 ml. of acid were added, and the liquid was evaporated on a steam-bath under diminished pressure to a thick viscous syrup. The latter was poured on twice its weight of sodium hydroxide pellets in a Claisen flask; when warmed gently the crude diethylhydrazine passed over at 85—100°. It was dried first over potassium hydroxide pellets (2 days) then over fused barium oxide. The dried product was distilled through a vacuum-jacketed Widmer column in an all-glass apparatus, and the fraction, b. p. 95—99° (50 g.), was collected, set aside for several days over fused barium oxide, and then fractionated as before; pure diethylhydrazine, b. p. 99·5—100°/762 mm., was the sole product and was collected in a receiver fitted with a barium oxide guard tube. It had d_4^{20} 0·7988, n_D^{20} 1·4214.

(ii) The compound could also be prepared by the reduction of diethylnitrosamine with lithium aluminium hydride. Finely-powdered lithium aluminium hydride (10 g.) was stirred for several minutes with sodium-dried ether (600 ml.) and a solution of diethylnitrosamine (23·5 g.) in anhydrous ether (135 ml.) was then added, with stirring, at a rate of about 2 drops per second; refluxing of the ether began after 20 minutes, and the rate of addition was adjusted so as to keep the reaction under control. A white solid was deposited gradually, the addition was complete in 1 hour, and stirring was continued for 15 minutes more. Water (25 ml.) was then added very cautiously with vigorous stirring during 1 hour; this was followed by 10N-sodium hydroxide (50 ml.) and, after being stirred for a further 10 minutes, the mixture was filtered and the residue was washed with ether (2 × 50 ml.). The combined filtrate and washings were dried (KOH pellets, followed by anhydrous $CaSO_4$) and fractionated through a 10″ vacuum-jacketed Widmer column; the diethylhydrazine (10 g.) was collected at 98·5—99·5°/760 mm. The crude product had d_4^{20} 0·7998, n_D^{20} 1·4201, and was evidently of high purity.

NN-*Di*-n-*propylhydrazine*. (i) Di-*n*-propylnitrosamine (41 g.) (XXIII, **575**) was dissolved in glacial acetic acid (210 ml.) and zinc powder (95%; 83 g.) added in small portions, with stirring, during 4 hours whilst the temperature was kept at 20—25°. Stirring was continued at 45—50° for 1 hour, and the mixture was filtered hot and washed with a little cold water. The filtrate was treated with 50% sodium hydroxide solution until the precipitate just redissolved, and the upper layer was separated. The preparation was repeated and the combined upper layers were dried (KOH pellets, 1 day; fresh KOH pellets, 1 week; fused BaO, 2 days) and distilled through a lagged Widmer column: the crude di-*n*-propylhydrazine (41 ml.), b. p. 135—140°, was dried (fused BaO, 8 weeks) and again fractionated. The pure *di*-n-*propylhydrazine* passed over at 140·5—141°/760 mm. and had d_4^{20} 0·8011, n_D^{20} 1·4265 (Found: C, 62·3; H, 13·9; N,

24·0. $C_8H_{18}N_2$ requires C, 62·1; H, 13·8; N, 24·1%). For the physical measurements the sample was distilled under diminished pressure in dry nitrogen; it had b. p. 31·5°/7 mm., d_4^{20} 0·7997, and n_D^{20} 1·4266.

(ii) Di-*n*-propylnitrosamine (29·5 g.) in anhydrous ether (200 ml.) was reduced with powdered lithium aluminium hydride (10 g.) in anhydrous ether (600 ml.) as detailed under diethylhydrazine. Stirring was continued for 8 hours after the nitrosamine had been added and the mixture was kept overnight. After decomposition of the excess of lithium aluminium hydride with water (35 ml.), and working up as before, pure di-*n*-propylhydrazine (20 g.), b. p. 140·5—141°/768 mm., d_4^{20} 0·8011, n_D^{20} 1·4266, was obtained.

NN-*Di*-n-*butylhydrazine*. The reduction of di-*n*-butylnitrosamine (XXIII, **576**) with zinc and acetic acid always gave mixtures of di-*n*-butylamine and di-*n*-butylhydrazine (the former predominating), which could not be separated satisfactorily by fractional distillation. The presence of di-*n*-butylhydrazine in the mixture was established by the addition of ethyl oxalate whereupon oxalic acid bis-*NN*-di-*n*-butylhydrazide slowly separated as needles, in poor yield (cf. Franchimont and van Erp, *Rec. Trav. chim.*, 1895, **14**, 318): these melted at 170° after recrystallisation from rectified spirit (Found: C, 63·1; H, 11·5. Calc. for $C_{18}H_{38}O_2N_4$: C, 63·1; H, 11·8%).

The compound was readily obtained by reduction of di-*n*-butylnitrosamine (36 g.) in anhydrous ether (205 ml.) with lithium aluminium hydride (10 g.) in anhydrous ether (600 ml.) for 5 hours as detailed for di-*n*-propylhydrazine. *Di*-n-*butylhydrazine* (15 g.), b. p. 60—62°/11 mm., d_4^{20} 0·8029, n_D^{20} 1·4325, was obtained; it boiled largely at 61°/8 mm. on redistillation (Found: C, 66·8; H, 13·8; N, 19·1. $C_8H_{20}N_2$ requires C, 66·6; H, 14·0; N, 19·4%).

NN-*Di*-n-*amylhydrazine*. Di-*n*-amylnitrosamine (30 g.; for preparation, see below) was reduced with lithium aluminium hydride (7·1 g.) as described above. The pure *hydrazine*, b. p. 87°/7 mm. (18 g.), was obtained as a colourless liquid on rapid distillation under reduced pressure (Found: C, 70·0; H, 14·3. $C_{10}H_{24}N_2$ requires C, 69·7; H, 14·0%) and its physical properties were determined immediately. After 1 day in a vacuum desiccator over fused barium oxide, it acquired a pale yellow colour and had d_4^{20} 0·8148, n_D^{20} 1·4390.

Di-n-*amylnitrosamine*. Redistilled di-*n*-amylamine (Light) (30 g.) was mixed with absolute ethyl alcohol (12 ml.), and 5N-hydrochloric acid was added, with stirring, until the solution was neutral to methyl orange; warming may be necessary to prevent crystallisation of the hydrochloride. The solution of the hydrochloride was added to one of sodium nitrite (22·5 g.) in water (25 ml.), and the mixture was heated, with vigorous stirring, to the boiling point and then refluxed gently for 45 minutes. After cooling, the upper oily layer was separated and heated rapidly over a gauze; about 5 ml. of impure alcohol distilled at 80—100° and a little solid (probably salt) appeared. The heating was discontinued and the solid separated; the residual yellow oil was distilled under reduced pressure giving *di*-n-*amylnitrosamine* (20 g.), b. p. 130—133°/10 mm. On redistillation from an all-glass apparatus this boiled largely at 130·5°/12 mm. (Found: C, 64·5; H, 11·9; N, 15·1. $C_{10}H_{22}ON_2$ requires C, 64·5; H, 11·8; N, 15·4%).

Di-n-*hexylnitrosamine*. Prepared similarly this *nitrosamine* had b. p. 155°/11 mm. (Found: C, 67·3; H, 12·2; N, 13·4. $C_{12}H_{26}ON_2$ requires C, 67·7; H, 12·2; N, 13·2%).

Aliphatic Ketazines.—Dimethyl, ethyl methyl, diethyl, methyl *n*-propyl, ethyl *n*-propyl, and di-*n*-propyl ketazine were prepared by heating the corresponding ketone under reflux with a 49% solution of hydrazine hydrate; alcohol was used to effect dissolution in the preparation of all except the first-named ketazine. The reaction mixture was subsequently treated with excess of potassium carbonate, whereupon the crude ketazine either separated or was obtained by ether extraction, and was purified by distillation.

Diethyl ketazine had b. p. 196°/757 mm. (Curtius and Thun, *J. pr. Chem.*, 1891, **44**, 161, give b. p. 190—195°; Mailhe, *Bull. Soc. chim.*, 1920, **27**, 541, erroneously gives b. p. 160—163°).

β-*Monoalkylaminopropionitriles*.—Redistilled acrylonitrile was treated with an excess of the corresponding monoalkylamine with stirring at <30°. After a further period of stirring, the mixture was heated at 100° for 1—2 hours and then treated with anhydrous potassium carbonate, the oil so obtained was distilled. The following propionitriles were so obtained: β-ethylamino-, b. p. 78—79°/11 mm. (cf. Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725, who give b. p. 92—95° (30 mm.); β-*n*-propylamino-, b. p. 91—92°/11—12 mm. (cf. Tarbell, Shakespeare, Claus, and Burnett, *ibid.*, 1946, **68**, 127, who give b. p. 119—121°/30 mm.); β-*n*-butylamino-, b. p. 100°/9 mm.; β-*n*-amylamino-, b. p. 114°/10 mm. (cf. Burckhalter, Jones, Holcomb, and Sweet, *ibid.*, 1943, **65**, 2012, who give b. p. 112—113°/10 mm.); and β-n-*hexylamino-propionitrile*, b. p. 126°/9 mm. (25 g. from 11·2 g. of acrylonitrile and 32 g. of *n*-hexylamine) (Found: C, 69·6; H, 11·9; N, 18·2. $C_9H_{18}N_2$ requires C, 70·0; H, 11·8; N, 18·2%).

β-*Dialkylaminopropionitriles.*—Heating a mixture of redistilled acrylonitrile with an excess of dialkylamine at 50° for 24 hours, followed by storage for 2 days at laboratory temperature, removal of the excess of amine, and distillation of the residue at reduced pressure gave the following β-dialkylaminopropionitriles: β-diethylamino-, b. p. 76°/11 mm. (cf. Whitmore *et al., loc. cit.*, who give b. p. 104—106°/35 mm.); β-di-*n*-propylamino-, b. p. 105—106°/11 mm. (cf. Whitmore *et al., loc. cit.*, who give b. p. 116°/20 mm.); β-di-*n*-butylamino-, b. p. 120°/10 mm.; and β-di-*n*-amylamino-propionitrile, b. p. 149°/8 mm. (Holcomb and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1309, give b. p. 136°/6 mm.).

β-*Alkoxypropionitriles.*—β-*Methoxy-* (b. p. 165·5°/759 mm.) *and* β-*ethoxy-propionitrile* (b. p. 173°/756 mm.; 58°/10 mm.). These were prepared by MacGregor and Pugh's method (*J.*, 1945, 535).

β-n-*Propoxypropionitrile.* Acrylonitrile (26·5 g.) was added at <45° to a solution of potassium hydroxide (0·15 g.) in *n*-propyl alcohol (33 g.), with stirring during 25 minutes. The mixture was heated under reflux at 100° for 1 hour and then allowed to cool. After the removal of a small quantity of brown solid, distillation gave the required nitrile (36·5 g.), which had b. p. 73·5°/10 mm. when pure (Christian and Hixon, *J. Amer. Chem. Soc.*, 1948, **70**, 133, give b. p. 87—89°/24 mm.).

β-n-*Butoxy-*, β-n-*amyloxy-, and* β-n-*hexyloxy-propionitrile.* These were prepared in a manner similar to that described for the *n*-propoxy-compound. β-n-*Hexyloxypropionitrile* [32 g.; from *n*-hexyl alcohol (67 g.), acrylonitrile (35 g.), and sodium (0·05 g.), under reflux for 18 hours] had b. p. 115·5°/9 mm. after redistillation (Found: C, 69·9; H, 11·2. $C_9H_{17}ON$ requires C, 69·9; H, 11·0%).

All the above nitriles remained colourless after several months' storage.

Dialkyl Azodiformates.—Diethyl azodiformate. This was prepared as detailed in *Org. Synth.*, 1948, **28**, 58.

Di-n-*propyl azodiformate.* This was prepared similarly from 90% hydrazine hydrate (11·5 g.) in alcohol (102 ml.), *n*-propyl chloroformate (b. p. 113—115°; 49·2 g.), and a solution of sodium carbonate (21·4 g.) in water (100 ml.) except that, after all the reactants had been added, stirring was continued for 7 hours. The upper oily layer was then separated, and the aqueous layer was extracted with ether (4 × 50 ml.). The combined extracts and upper layer were dried ($MgSO_4$), and the solvents removed first on a steam-bath and then under reduced pressure. The residue (32 g.) solidified on cooling and melted at 58—59°; the m. p. was raised to 63—64° on recrystallisation from benzene–light petroleum (b. p. 60—80°) (Boehm and Mehta, *Ber.*, 1938, **71**, 1797, give m. p. 63—64°).

This hydrazodiformate (28 g.), suspended in a mixture of water (150 ml.) and benzene (150 ml.), was oxidised with chlorine following the procedure used for the diethyl compound. *Di*-n-*propyl azodiformate* (23 g.), a red liquid, b. p. 121—123°/11 mm., was obtained (Found: C, 47·8; H, 7·1. $C_8H_{14}O_4N_2$ requires C, 47·5; H, 7·0%). A middle fraction, b. p. 122°/11 mm., was employed for the physical measurements.

Di-n-*butyl azodiformate.* This was prepared from *n*-butyl chloroformate (b. p. 136—138°, rapid distillation; 45·5 g.) as described for the di-*n*-propyl compound. The resulting hydrazodiformate (33 g.; m. p. 46°) was oxidised with chlorine and gave *di*-n-*butyl azodiformate* (22 g.), b. p. 142—144°/11 mm. (Found: C, 51·8; H, 8·1. $C_{10}H_{18}O_4N_2$ requires C, 52·1; H, 7·9%). Redistillation gave a main fraction, b. p. 142°/11 mm.

Dialkyl Carbonates.—These were prepared by heating alkyl chloroformates and the appropriate alcohols under reflux (for the times given below in parentheses). Ethyl, *n*-propyl, and *n*-butyl chloroformate were obtained from Messrs. Light, and *n*-amyl and *n*-hexyl chloroformate from Eastman Kodak. They were all purified by fractional distillation immediately before use: two rapid distillations gave better results than one slow, careful fractionation (cf. Chattaway and Saerens, *J.*, 1920, **117**, 708).

Di-n-*butyl carbonate.* *n*-Butyl chloroformate (47 g.) and anhydrous *n*-butyl alcohol (51 g.) were refluxed for 3 hours. Hydrogen chloride was freely evolved during the first 2 hours and then slackened. Upon distillation a fraction (33 g.), b. p. 115—140°, composed of mixed reactants, passed over first, followed by the di-*n*-butyl carbonate at 202—205°/750 mm. (46 g.). Redistillation gave the pure product, b. p. 204·5°/755 mm., d_4^{20} 0·9249, n_D^{20} 1·4118. The Eastman Kodak product when purified (XXIII, **594**) had b. p. 204·5°/758 mm., d_4^{20} 0·9251, n_D^{20} 1·4117.

Di-n-*amyl carbonate.* *n*-Amyl chloroformate (50 g.; b. p. 39—40°/9 mm., d_4^{20} 1·0241, n_D^{20} 1·4180) and pure *n*-amyl alcohol (51 g.) were refluxed for 3 hours, by which time the smell of the former could no longer be detected. On distillation, di-*n*-amyl carbonate (41 g.), b. p. 237—239°/754 mm., was collected. Redistillation gave a main fraction of b. p. 238·5°/757 mm.

Di-n-*hexyl carbonate.* *n*-Hexyl chloroformate (49·3 g.; b. p. 64—65°/10 mm., d_4^{20} 1·0113, n_D^{20} 1·4236) and pure *n*-hexyl alcohol (61·2 g.) gave, on distillation after 12 hours' refluxing, di-*n*-hexyl carbonate (55 g.), b. p. 266—269°/762 mm. and 146·5°/9 mm. on redistillation.

Ethyl n-*propyl carbonate.* Ethyl chloroformate (54·3 g.; b. p. 93°/753 mm., d_4^{20} 1·1356, n_D^{20} 1·3952) was heated to gentle boiling and treated during 1 hour with anhydrous *n*-propyl alcohol (30 g.). Refluxing was continued for 2·5 hours by which time the evolution of hydrogen chloride had slackened considerably. The mixture was fractionated through a Dufton column, giving a low-boiling fraction (20 g.) and then ethyl *n*-propyl carbonate (40·5 g.), b. p. 146°/758 mm. Redistillation gave the pure compound, b. p. 145·5°/760 mm.

n-*Butyl ethyl carbonate.* Anhydrous *n*-butyl alcohol (37 g.) was added during 90 minutes to ethyl chloroformate, (54·3 g.) and the mixture was refluxed for 2 hours. Fractionation gave *n*-butyl ethyl carbonate (31 g.), b. p. 166—167°/759 mm.; this boiled largely at 167°/759 mm. on redistillation (Chattaway and Saerens, *loc. cit.*, give b. p. 168·5°/748 mm.).

n-*Amyl ethyl carbonate.* Anhydrous *n*-amyl alcohol (44 g.) was added during 60 minutes to boiling ethyl chloroformate (53·4 g.) and the mixture was refluxed for 2 hours. Fractionation gave n-*amyl ethyl carbonate* (36 g.) b. p. 187—189°/760 mm. (Found: C, 60·2; H, 10·0. $C_9H_{16}O_3$ requires C, 60·0; H, 10·0%). This boiled largely at 188°/760 mm. on redistillation.

Ethyl n-*hexyl carbonate.* Pure *n*-hexyl alcohol (51 g.) was added during 90 minutes to boiling ethyl chloroformate (54·3 g.), and the mixture was refluxed for 4 hours. Fractionation gave *ethyl* n-*hexyl carbonate* (32 g.), b. p. 205—207°/764 mm. (Found: C, 62·3; H, 10·4. $C_9H_{18}O_3$ requires C, 62·1; H, 10·4%). This boiled largely at 206·5°/764 mm. on redistillation.

n-*Butyl* n-*propyl carbonate.* *n*-Butyl chloroformate (68·3 g.; b. p. 46—47°/28 mm., d_{40}^{2} 1·0558, n_D^{20} 1·4118) was added during 90 minutes to boiling anhydrous *n*-propyl alcohol (30 g.). After refluxing for a further 3 hours, the mixture was fractionated through a Dufton column whereupon *n*-butyl *n*-propyl carbonate (49 g.), b. p. 186—187°/764 mm., was obtained. On redistillation, the main fraction of b. p. 187°/764 mm. was collected (Chattaway and Saerens, *loc. cit.*, give b. p. 187·5°/752 mm.).

n-*Heptyl cyanide.* A mixture of sodium cyanide (15·2 g.) in water (20 ml.) and *n*-heptyl iodide (57 g.) in methanol (75 ml.) was refluxed for 28 hours, and methanol (60 ml.) then removed by fractionation. The residue was treated with water, and the upper layer of crude nitrile washed twice with half its volume of concentrated hydrochloric acid by shaking it for 0·5 and 2 hours, thrice with water, then with saturated sodium hydrogen carbonate solution, and finally with water; it was then dried (anhydrous $MgSO_4$) and distilled (yield 29 g.). The high density of a middle fraction suggested the presence of a little iodide; the product in methanol (100 ml.) was accordingly heated under reflux for 12 hours with sodium cyanide (10 g.) in water (15 ml.), and the *n*-heptyl cyanide then isolated as before; b. p. 82·5°/10 mm., d_4^{20} 0·8141, n_D^{20} 1·4206 (Merckx, Verhulst, and Bruylants, *Bull. Soc. chim. Belg.*, 1933, **42**, 177, found b. p. 82°/10 mm., d_4^{20} 0·8136, n_D^{20} 1·4202, interpolated from values at 15° and 30°).

n-*Octyl cyanide.* This was prepared from n-octyl bromide (65 g.) and sodium cyanide (20·1 g.) as described for n-heptyl cyanide. The product was redistilled from phosphoric oxide (10 g.), then refluxed with thionyl chloride (20 g.) for 1 hour, and again treated with aqueous sodium cyanide for 11 hours; the alcohol was distilled off and the residue dissolved in ether. The ethereal solution was shaken with concentrated hydrochloric acid (2 × 20 ml.) for 1-hour periods, washed with water, sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). The residue left when the ether was removed was refluxed for 1 hour with thionyl chloride (20 g.), the excess of the latter distilled off at atmospheric pressure, and the residual liquid distilled under reduced pressure, giving *n*-octyl cyanide (14 g.), a middle fraction of which had b. p. 100°/11 mm., d_4^{20} 0·8164, n_D^{20} 1·4258 (Merckx, Verhulst, and Bruylants, *loc. cit.*, find b. p. 98·5°/10 mm., d_4^{20} 0·8169, n_D^{20} 1·4252, interpolated).

607. *Acetaldoxime.* B. p. 115°/762 mm.; *M* 59·07; n_C 1·42452, n_D 1·42636, n_F 1·43340, $n_{G'}$ 1·43884; R_C 15·65, R_D 15·71, R_F 15·94, $R_{G'}$ 16·11; Mn_D^{20} 84·26. Densities determined: d_4^{20} 0·9640, $d_4^{39·7}$ 0·9462, $d_4^{59·5}$ 0·9278.

t	*H*	d_4^t	γ	*P*	*t*	*H*	d_4^t	γ	*P*
22·2°	14·20	0·9620	31·80	145·8	60·2°	12·72	0·9272	27·46	145·8
40·0	13·42	0·9459	29·55	145·6				Mean	145·7

608. *Propaldoxime.* B. p. 134°/761 mm.; *M* 73·10; n_C 1·42750, n_D 1·43028, n_F 1·43703, $n_{G'}$ 1·44228; R_C 20·23, R_D 20·35, R_F 20·62, $R_{G'}$ 20·84; Mn_D^{20} 104·55. Densities determined: d_4^{20} 0·9286, $d_4^{40·6}$ 0·9091, $d_4^{60·2}$ 0·8912, $d_4^{85·3}$ 0·8664.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
14·9°	13·97	0·9324	30·36	183·8	41·7°	13·08	0·9081	27·65	184·6
19·8	13·77	0·9288	29·78	183·9	61·4	12·24	0·8901	25·37	184·3
								Mean	184·2

609. n-*Butaldoxime*. B. p. 151°/750 mm.; M 87·12; n_C 1·43358, n_D 1·43670, n_F 1·44303, $n_{G'}$ 1·44830; R_C 24·90, R_D 25·06, R_F 25·37, $R_{G'}$ 25·64; Mn_D^{20} 125·17. Densities determined: d_4^{20} 0·9103, $d_4^{40·4}$ 0·8927, $d_4^{60·2}$ 0·8762, $d_4^{85·1}$ 0·8534.

21·4°	13·63	0·9081	28·82	222·8	60·5°	12·34	0·8759	25·16	222·8
40·4	12·97	0·8927	26·96	222·4	85·8	11·54	0·8528	22·86	223·5
								Mean	222·9

610. *Ethyl methyl ketoxime*. B. p. 151·5°/770 mm.; M 87·12; n_C 1·44027, n_D 1·44310, n_F 1·44997, $n_{G'}$ 1·45530; R_C 24·88, R_D 25·01, R_F 25·35, R_G 25·60; Mn_D^{20} 125·72. Densities determined: d_4^{20} 0·9238, $d_4^{41·0}$ 0·9055, $d_4^{60·5}$ 0·8887, $d_4^{86·5}$ 0·8645.

16·0°	14·03	0·9273	30·29	220·4	60·4°	12·43	0·8888	25·72	220·7
19·1	13·93	0·9246	29·99	220·5	85·3	11·51	0·8656	23·20	220·9
41·2	13·08	0·9053	27·57	220·5					
								Mean	220·6

611. *Methyl* n-*propyl ketoxime*. B. p. 168°/754 mm.; M 101·15; n_C 1·44252, n_D 1·44546, n_F 1·45205, n_G 1·45278; R_C 29·49, R_D 29·67, R_F 30·05, $R_{G'}$ 30·34; Mn_D^{20} 146·21. Densities determined: d_4^{20} 0·9083, $d_4^{41·0}$ 0·8905, $d_4^{60·9}$ 0·8738, $d_4^{86·3}$ 0·8517.

18·9°	13·77	0·9092	29·15	258·5	61·0°	12·28	0·8737	24·98	258·8
41·7	12·90	0·8898	26·72	258·5	87·1	11·49	0·8511	22·77	259·6
								Mean	258·8

612. *Diethyl ketoxime*. B. p. 165·5°/765 mm.; M 101·15; n_C 1·44337, n_D 1·44651, n_F 1·45282, $n_{G'}$ 1·45820; R_C 29·42, R_D 29·60, R_F 29·96, $R_{G'}$ 30·26; Mn_D^{20} 146·31. Densities determined: d_4^{20} 0·9123, $d_4^{40·2}$ 0·8962, $d_4^{60·4}$ 0·8786, $d_4^{86·1}$ 0·8567.

25·1°	13·62	0·9082	28·80	258·0	61·2°	12·33	0·8779	25·20	258·2
40·5	12·98	0·8960	27·08	257·5	85·7	11·44	0·8570	22·83	258·0
								Mean	257·9

613. *Ethyl* n-*propyl ketoxime*. B. p. 180°/753 mm.; M 115·17; n_C 1·44372, n_D 1·44701, n_F 1·45302, $n_{G'}$ 1·45816; R_C 33·96, R_D 34·18, R_F 34·58, $R_{G'}$ 34·92; Mn_D^{20} 166·65. Densities determined: d_4^{20} 0·9002, $d_4^{41·4}$ 0·8829, $d_4^{60·0}$ 0·8672, $d_4^{85·1}$ 0·8466.

17·1°	13·80	0·9025	29·00	296·1	60·8°	12·39	0·8666	25·00	297·2
41·8	12·98	0·8826	26·67	296·5	86·3	11·53	0·8456	22·70	297·3
								Mean	296·8

614. *Di*-n-*propyl ketoxime*. B. p. 194·5—195°/755 mm.; M 129·20; n_C 1·44440, n_D 1·44746, n_F 1·45357, $n_{G'}$ 1·45888; R_C 38·58, R_D 38·81, R_F 39·27, $R_{G'}$ 39·66; Mn_D^{20} 187·02. Densities determined: d_4^{20} 0·8903, $d_4^{40·0}$ 0·8748, $d_4^{85·7}$ 0·8381.

19·4°	13·43	0·8908	27·85	333·2	61·1°	12·20	0·8581	24·37	334·5
40·4	12·80	0·8745	26·06	333·8	86·8	11·38	0·8372	22·18	333·0
								Mean	333·6

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
20·5°	5135	0·8899	1·0148	28·10	334·3	60·7°	4459	0·8584	1·0164	24·44	334·7
40·4	4775	0·8745	1·0156	26·15	334·1	85·7	4053	0·8381	1·0176	22·24	334·8
										Mean	334·5

615. *Acetoxime* O-*methyl ether*. B. p. 73°/760 mm.; M 87·12; n_C 1·39797, n_D 1·40052, n_F 1·40673, $n_{G'}$ 1·41153; R_C 25·15, R_D 25·29, R_F 25·63, $R_{G'}$ 25·90; Mn_D^{20} 122·01. Densities determined: d_4^{20} 0·8361, $d_4^{41·1}$ 0·8126.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
17·9°	11·82	0·8385	23·07	227·9	42·3°	10·84	0·8113	20·48	228·7
								Mean	228·3

616. *Acetoxime* O-*ethyl ether*. B. p. 93°/760 mm.; M 101·15; n_C 1·40176, n_D 1·40420, n_F 1·41033, $n_{G'}$ 1·41499; R_C 29·95, R_D 30·11, R_F 30·51, $R_{G'}$ 30·82; Mn_D^{20} 142·04. Densities determined: d_4^{20} 0·8219, $d_4^{40·5}$ 0·8010, $d_4^{60·9}$ 0·7795.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
21·4°	11·69	0·8205	22·33	268·0	60·2°	9·93	0·7802	18·04	267·6
41·0	10·83	0·8005	20·18	268·0				Mean	267·9

617. *Acetoxime* O-n-*propyl ether.* B. p. 116°/750 mm.; M 115·17; n_C 1·40920, n_D 1·41196, n_F 1·41784, $n_{G'}$ 1·42247; R_C 34·44, R_D 34·64, R_F 35·07, $R_{G'}$ 35·42; Mn_D^{20} 162·74. Densities determined: d_4^{20} 0·8272, $d_4^{41·0}$ 0·8063, $d_4^{60·9}$ 0·7865.

16·9°	12·39	0·8303	23·95	306·9	60·9°	10·53	0·7865	19·28	306·9
40·3	11·46	0·8070	21·53	307·4				Mean	307·1

618. *Ethyl methyl ketoxime* O-*ethyl ether.* B. p. 113°/761 mm.; M 115·17; n_C 1·40894, n_D 1·41152, n_F 1·41747, $n_{G'}$ 1·42198; R_C 34·48, R_D 34·67, R_F 35·12, $R_{G'}$ 35·45; Mn_D^{20} 162·56. Densities determined: d_4^{20} 0·8256, $d_4^{40·2}$ 0·8045, $d_4^{60·4}$ 0·7837, $d_4^{84·2}$ 0·7585.

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
18·0°	4357	0·8269	1·0162	23·88	307·9	59·5°	3546	0·7846	1·0189	19·49	308·4
39·9	3927	0·8052	1·0175	21·55	308·2	85·2	3049	0·7574	1·0212	16·75	307·6
										Mean	308·0

619. *Ethyl methyl ketoxime* O-n-*propyl ether.* B. p. 136°/756 mm.; M 129·20; n_C 1·41637, n_D 1·41896, n_F 1·42504, $n_{G'}$ 1·42961; R_C 38·89, R_D 39·11, R_F 39·60, $R_{G'}$ 39·97; Mn_D^{20} 183·33. Densities determined: d_4^{20} 0·8343, $d_4^{40·2}$ 0·8156, $d_4^{60·7}$ 0·7968, $d_4^{86·0}$ 0·7712.

17·8°	4422	0·8364	1·0161	24·23	342·7	61·0°	3659	0·7965	1·0186	20·10	343·5
40·6	3969	0·8152	1·0175	21·78	342·4	85·0	3130	0·7721	1·0210	17·23	341·7
										Mean	342·6

620. *Diethyl ketoxime* O-*ethyl ether.* B. p. 132·5°/764 mm.; M 129·20; n_C 1·41608, n_D 1·41861, n_F 1·42467, $n_{G'}$ 1·42931; R_C 39·01, R_D 39·22, R_F 39·72, $R_{G'}$ 40·10; Mn_D^{20} 183·28. Densities determined: d_4^{20} 0·8312, $d_4^{42·2}$ 0·8106, $d_4^{61·6}$ 0·7917, $d_4^{84·7}$ 0·7692.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
15·1°	12·54	0·8359	24·40	343·5	61·1°	10·66	0·7921	19·66	343·5
20·5	12·22	0·8307	23·63	342·9	86·9	9·55	0·7671	17·06	342·3
41·0	11·43	0·8117	21·60	343·2				Mean	343·1

621. *Diethyl ketoxime* O-n-*propyl ether.* B. p. 153·5—154°/760 mm.; M 143·23; n_C 1·42110, n_D 1·42361, n_F 1·42970, $n_{G'}$ 1·43437; R_C 43·57, R_D 43·80, R_F 44·35, $R_{G'}$ 44·77; Mn_D^{20} 203·90. Densities determined: d_4^{20} 0·8338, $d_4^{41·6}$ 0·8143, $d_4^{60·6}$ 0·7974, $d_4^{85·9}$ 0·7737.

21·0°	12·67	0·8329	24·57	382·9	60·7°	11·18	0·7973	20·75	383·4
41·4	11·93	0·8145	22·62	383·5	85·8	10·10	0·7738	18·20	382·3
								Mean	383·0

622. *Methyl* n-*propyl ketoxime* O-*ethyl ether.* B. p. 134°/754 mm.; M 129·20; n_C 1·41582, n_D 1·41836, n_F 1·42441, $n_{G'}$ 1·42909; R_C 39·15, R_D 39·36, R_F 39·85, $R_{G'}$ 40·24; Mn_D^{20} 183·26. Densities determined: d_4^{20} 0·8279, $d_4^{40·4}$ 0·8094, $d_4^{60·8}$ 0·7893, $d_4^{85·3}$ 0·7649.

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
18·4°	4424	0·8294	1·0160	23·69	343·7	60·0°	3569	0·7902	1·0189	19·61	344·1
39·5	3961	0·8103	1·0175	21·73	344·3	86·0	3132	0·7642	1·0208	17·24	344·5
										Mean	344·2

623. *Methyl* n-*propyl ketoxime* O-n-*propyl ether.* B. p. 155°/746 mm.; M 143·22; n_C 1·42055, n_D 1·42306, n_F 1·42912, $n_{G'}$ 1·43385; R_C 43·64, R_D 43·87, R_F 44·41, $R_{G'}$ 44·85; Mn_D^{20} 203·82. Densities determined: d_4^{20} 0·8315, $d_4^{40·0}$ 0·8129, $d_4^{60·8}$ 0·7962, $d_4^{86·0}$ 0·7694.

17·8°	4561	0·8334	1·0156	24·99	384·1	60·7°	3741	0·7962	1·0182	20·53	382·8
39·5	4096	0·8130	1·0169	22·47	383·4	86·5	3293	0·7694	1·0199	18·11	384·0
										Mean	383·6

624. *Ethyl* n-*propyl ketoxime* O-*ethyl ether.* B. p. 152°/770 mm.; M 143·23; n_C 1·42010, n_D 1·42261, n_F 1·42870, $n_{G'}$ 1·43329; R_C 43·78, R_D 44·00, R_F 44·56, $R_{G'}$ 44·97; Mn_D^{20} 203·76. Densities determined: d_4^{20} 0·8282, $d_4^{40·0}$ 0·8105, $d_4^{62·2}$ 0·7905, $d_4^{86·8}$ 0·7678.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
17·3°	12·69	0·8306	24·54	383·8	61·5°	10·94	0·7911	20·15	383·6
41·0	11·77	0·8096	22·19	384·0	87·0	9·93	0·7676	17·75	383·1
								Mean	383·6

625. *Ethyl* n-*propyl ketoxime* O-n-*propyl ether*. B. p. 170·5°/760 mm.; *M* 157·25; n_C 1·42421, n_D 1·42671, n_F 1·43286, $n_{G'}$ 1·43733; R_C 48·33, R_D 48·58, R_F 49·20, $R_{G'}$ 49·64; Mn_D^{20} 224·35. Densities determined: d_4^{20} 0·8305, $d_4^{40·0}$ 0·8135, $d_4^{60·6}$ 0·7958, $d_4^{86·3}$ 0·7734.

t	*H*	d_4^t	γ	*P*	*t*	*H*	d_4^t	γ	*P*
20·3°	12·86	0·8302	24·86	422·9	59·6°	11·33	0·7967	21·02	422·7
40·2	12·20	0·8133	23·10	423·9	86·7	10·24	0·7730	18·43	421·5
								Mean	422·8

626. *Di*-n-*propyl ketoxime* O-*ethyl ether*. B. p. 170·5°/765 mm.; *M* 157·25; n_C 1·42386, n_D 1·42636, n_F 1·43253, $n_{G'}$ 1·43638; R_C 48·40, R_D 48·65, R_F 49·26, $R_{G'}$ 49·68; Mn_D^{20} 224·30. Densities determined: d_4^{20} 0·8288, $d_4^{40·0}$ 0·8121, $d_4^{61·8}$ 0·7932, $d_4^{86·3}$ 0·7718.

20·1°	12·72	0·8287	24·54	422·3	61·5°	11·13	0·7935	20·56	422·0
43·2	11·93	0·8094	22·48	423·0	86·6	10·13	0·7715	18·20	421·0
								Mean	421·1

627. *Di*-n-*propyl ketoxime* O-n-*propyl ether*. B. p. 187°/749 mm.; *M* 171·28; n_C 1·42824, n_D 1·43073, n_F 1·43683, $n_{G'}$ 1·44143; R_C 53·04, R_D 53·31, R_F 53·96, $R_{G'}$ 54·46; Mn_D^{20} 234·02. Densities determined: d_4^{20} 0·8312, $d_4^{41·7}$ 0·8127, $d_4^{61·0}$ 0·7963, $d_4^{86·9}$ 0·7739.

21·0°	12·92	0·8303	24·98	461·2	61·0°	11·35	0·7963	21·04	460·7
40·6	12·14	0·8136	23·00	461·0	87·3	10·50	0·7739	18·92	461·6
								Mean	461·1

628. NN-*Diethylhydrazine*. B. p. 99·5—100°/762 mm.; *M* 88·16; n_C 1·41860, n_D 1·42136, n_F 1·42745, $n_{G'}$ 1·43225; R_C 27·85, R_D 28·01, R_F 28·37, $R_{G'}$ 28·64; Mn_D^{20} 125·31. Densities determined: d_4^{20} 0·7988, $d_4^{41·3}$ 0·7791, $d_4^{59·7}$ 0·7623.

24·4°	13·20	0·7947	24·42	246·6	60·6°	11·66	0·7615	20·67	247·2
41·8	12·45	0·7786	22·57	247·0					
								Mean	246·9

629. NN-*Di*-n-*propylhydrazine*. B. p. 31·5°/7 mm.; *M* 116·21; n_C 1·42412, n_D 1·42661, n_F 1·43267, $n_{G'}$ 1·43716; R_C 37·09, R_D 37·29, R_F 37·75, $R_{G'}$ 38·09; Mn_D^{20} 165·79. Densities determined: d_4^{20} 0·7997, $d_4^{41·0}$ 0·7819, $d_4^{60·7}$ 0·7644.

24·5°	13·31	0·7959	24·66	325·4	61·0°	11·80	0·7641	20·99	325·5
41·1	12·70	0·7818	23·12	326·0					
								Mean	325·6

No measurements were carried out at 86° because of the slight decomposition due to prolonged heating at this temperature (small bubbles seen in the capillary tube of the surface-tension apparatus and in the pycnometer).

630. NN-*Di*-n-*butylhydrazine*. B. p. 61°/8 mm.; *M* 144·26; n_C 1·43184, n_D 1·43430, n_F 1·44033, $n_{G'}$ 1·44481; R_C 46·30, R_D 46·54, R_F 47·10, $R_{G'}$ 47·51; Mn_D^{20} 206·91. Densities determined: d_4^{20} 0·8078, $d_4^{40·0}$ 0·7924.

22·6°	13·82	0·8058	25·93	404·0	40·7°	13·17	0·7919	24·28	404·4
								Mean	404·2

631. NN-*Di*-n-*amylhydrazine*. B. p. 87°/7 mm.; *M* 172·31; n_C 1·43526, n_D 1·43771, n_F 1·44363, $n_{G'}$ 1·44818; R_C 55·49, R_D 55·76, R_F 56·42, $R_{G'}$ 56·92; Mn_D^{20} 247·73. Densities determined: d_4^{20} 0·8107, $d_4^{41·0}$ 0·7948, $d_4^{60·9}$ 0·7797.

16·1°	14·43	0·8137	27·34	484·2	61·1°	12·72	0·7795	23·08	484·5
41·0	13·46	0·7948	24·91	484·3					
								Mean	484·3

Slight decomposition occurred after prolonged heating at 60°; the measurements of surface tension and density were completed before decomposition was visible.

632. *Di*-n-*amylnitrosamine*. B. p. 130·5°/12 mm.; *M* 186·30; n_C 1·44831, n_D 1·45122, n_F 1·45839, $n_{G'}$ 1·46446; R_C 55·89, R_D 56·20, R_F 56·97, $R_{G'}$ 56·62; Mn_D^{20} 270·36. Densities determined: d_4^{20} 0·8930, $d_4^{40·7}$ 0·8776, $d_4^{61·0}$ 0·8627, $d_4^{87·3}$ 0·8436.

20·2°	14·58	0·8929	30·31	489·6	61·7°	13·35	0·8622	26·80	491·6
41·0	13·87	0·8774	28·33	389·9	86·3	12·59	0·8443	24·75	492·2
								Mean	490·8

633. *Di*-n-*hexylnitrosamine*. B. p. 155°/11 mm.; M 214·35; n_C 1·45042, n_D 1·45322, n_F 1·46026, $n_{G'}$ 1·46595; R_C 65·19, R_D 65·54, R_F 66·42, $R_{G'}$ 67·13; Mn_D^{20} 311·49. Densities determined: d_4^{20} 0·8844, $d_4^{40\cdot9}$ 0·8693, $d_4^{61\cdot0}$ 0·8551, $d_4^{86\cdot1}$ 0·8380.

t	H	d_4'	γ	P	t	H	d	γ	P
19·9°	14·62	0·8845	30·11	567·7	61·3°	13·38	0·8459	26·63	569·6
42·1	13·92	0·8685	28·15	568·4	86·7	12·59	0·8376	24·55	569·6
								Mean	569·6

634. *Di*-n-*hexylamine*. B. p. 236—236·5°/758 mm.; M 185·35; n_C 1·43209, n_D 1·43445, n_F 1·43999, $n_{G'}$ 1·44418; R_C 60·95, R_D 61·25, R_F 61·92, $R_{G'}$ 62·43; Mn_D^{20} 265·88. Densities determined: d_4^{20} 0·7889, $d_4^{41\cdot2}$ 0·7736, $d_4^{60\cdot1}$ 0·7596, $d_4^{84\cdot1}$ 0·7418.

t	Δp	d_4'	ϕ	γ	P	t	Δp	d_4'	ϕ	γ	P
23·5°	4958	0·7863	1·0135	27·10	537·8	60·4°	4328	0·7594	1·0150	23·69	538·5
40·5	4708	0·7741	1·0140	25·75	539·4	85·0	3957	0·7411	1·0160	21·68	539·7
										Mean	538·9

635. *Dimethyl ketazine*. B. p. 133°/763 mm.; M 112·18; n_C 1·44979, n_D 1·45347, n_F 1·46244, $n_{G'}$ 1·46979; R_C 35·78, R_D 36·04, R_F 36·65, $R_{G'}$ 37·15; Mn_D^{20} 163·05. Densities determined: d_4^{20} 0·8422, $d_4^{40\cdot1}$ 0·8242, $d_4^{60\cdot5}$ 0·8053.

t	H	d_4'	γ	P	t	H	d_4'	γ	P
20·3°	13·58	0·8419	26·62	302·7	62·0°	11·77	0·8043	22·04	302·2
41·1	12·76	0·8233	24·46	303·0				Mean	302·6

636. *Ethyl methyl ketazine*. B. p. 169°/765 mm.; M 140·23; n_C 1·45081, n_D 1·45417, n_F 1·46203, $n_{G'}$ 1·46930; R_C 45·00, R_D 45·30, R_F 46·02, $R_{G'}$ 46·59; Mn_D^{20} 203·92. Densities determined: d_4^{20} 0·8387, $d_4^{40\cdot2}$ 0·8215, $d_4^{60\cdot6}$ 0·8042, $d_4^{84\cdot5}$ 0·7829.

17·6°	13·73	0·8409	26·88	379·7	61·3°	12·02	0·8036	22·49	380·0
42·0	12·78	0·8200	24·40	380·1	84·5	11·21	0·7829	20·43	380·8
								Mean	380·2

637. *Methyl* n-*propyl ketazine*. B. p. 202°/757 mm.; M 168·28; n_C 1·45390, n_D 1·45712, n_F 1·46529, $n_{G'}$ 1·47175; R_C 54·30, R_D 54·63, R_F 55·47, $R_{G'}$ 56·14; Mn_D^{20} 245·20. Densities determined: d_4^{20} 0·8391, $d_4^{41\cdot2}$ 0·8217, $d_4^{59\cdot6}$ 0·8067, $d_4^{85\cdot3}$ 0·7857.

18·9°	13·87	0·8400	27·13	457·2	61·8°	12·26	0·8409	22·97	457·7
40·8	13·09	0·8220	25·05	458·0	88·5	11·26	0·7831	20·53	457·4
								Mean	457·6

638. *Diethyl ketazine*. B. p. 196°/757 mm.; M 168·28; n_C 1·45301, n_D 1·45672, n_F 1·46436, $n_{G'}$ 1·47104; R_C 54·08, R_D 54·46, R_F 55·25, $R_{G'}$ 55·92; Mn_D^{20} 245·13. Densities determined: d_4^{20} 0·8412, $d_4^{40\cdot6}$ 0·8244, $d_4^{60\cdot6}$ 0·8081, $d_4^{85\cdot9}$ 0·7878.

20·7°	13·56	0·8406	26·54	454·4	61·3°	12·11	0·8075	22·77	455·2
40·5	12·80	0·8247	24·58	454·3	86·9	11·19	0·7870	20·50	455·0
								Mean	454·7

639. *Ethyl* n-*propyl ketazine*. B. p. 97°/9 mm.; M 196·33; n_C 1·45441, n_D 1·45811, n_F 1·46547, $n_{G'}$ 1·47276; R_C 63·44, R_D 63·89, R_F 64·78, $R_{G'}$ 65·65; Mn_D^{20} 286·27. Densities determined: d_4^{20} 0·8387, $d_4^{40\cdot7}$ 0·8229, $d_4^{60\cdot9}$ 0·8086, $d_4^{85\cdot9}$ 0·7889.

21·3°	13·57	0·8377	26·47	531·6	60·7°	12·25	0·8081	23·05	532·3
40·5	12·96	0·8231	24·84	532·5	86·1	11·31	0·7887	20·77	531·4
								Mean	532·0

640. *Di*-n-*propyl ketazine*. B. p. 118°/7 mm.; M 224·38; n_C 1·45581, n_D 1·45951, n_F 1·46660, $n_{G'}$ 1·47284; R_C 72·85, R_D 73·34, R_F 74·31, $R_{G'}$ 75·16; Mn_D^{20} 327·48. Densities determined: d_4^{20} 0·8372, $d_4^{40\cdot1}$ 0·8229, $d_4^{60\cdot9}$ 0·8088, $d_4^{85\cdot7}$ 0·7893.

24·1°	13·56	0·8342	26·34	609·3	61·7°	12·15	0·8076	22·85	607·4
40·8	12·89	0·8224	24·68	608·1	87·1	11·40	0·7883	20·87	608·8
								Mean	608·4

641. β-*Ethylaminopropionitrile.* B. p. 78·5°/11 mm.; M 98·15; n_C 1·43031, n_D 1·43269, n_F 1·43865, $n_{G'}$ 1·44284; R_C 28·57, R_D 28·71, R_F 29·06, $R_{G'}$ 29·30; Mn_D^{20} 140·62. Densities determined: d_4^{20} 0·8878, $d_4^{40\cdot2}$ 0·8711, $d_4^{61\cdot4}$ 0·8534, $d_4^{85\cdot5}$ 0·8338.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
24·1°	15·78	0·8844	32·49	265·0	61·3°	14·48	0·8535	28·77	266·3
40·6	15·27	0·8708	30·96	265·9	87·1	13·64	0·8325	26·44	267·0
								Mean	266·6

642. β-n-*Propylaminopropionitrile.* B. p. 91°/11 mm.; M 112·16; n_C 1·43292, n_D 1·43535, n_F 1·44107, $n_{G'}$ 1·44547; R_C 33·23, R_D 33·40, R_F 33·78, $R_{G'}$ 34·07; Mn_D^{20} 160·99. Densities determined: d_4^{20} 0·8771, $d_4^{42\cdot6}$ 0·8598, $d_4^{60\cdot8}$ 0·8450, $d_4^{85\cdot6}$ 0·8245.

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
18·8°	5776	0·8780	1·0130	31·56	302·8	60·7°	5062	0·8451	1·0142	27·69	304·5
40·2	5399	0·8617	1·0136	29·51	303·4	85·6	4688	0·8245	1·0150	25·66	306·2
										Mean	304·2

643. β-n-*Butylaminopropionitrile.* B. p. 100°/9 mm.; M 126·20; n_C 1·43567, n_D 1·43801, n_F 1·44376, $n_{G'}$ 1·44812; R_C 37·75, R_D 37·93, R_F 38·36, $R_{G'}$ 38·68; Mn_D^{20} 181·48. Densities determined: d_4^{20} 0·8736, $d_4^{40\cdot6}$ 0·8572, $d_4^{61\cdot6}$ 0·8407, $d_4^{85\cdot6}$ 0·8217.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
16·2°	15·26	0·8766	31·14	340·1	61·0°	13·98	0·8412	27·38	343·2
40·3	14·56	0·8574	29·06	341·8	86·0	13·27	0·8214	25·44	345·6
								Mean	342·7

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
18·6°	5613	0·8746	1·0133	30·67	339·6	60·8°	4974	0·8413	1·0144	27·21	342·6
40·2	5285	0·8575	1·0138	28·90	341·2	84·8	4592	0·8223	1·0153	25·14	343·7
										Mean	341·8

644. β-n-*Amylaminopropionitrile.* B. p. 114°/10 mm.; M 140·23; n_C 1·43787, n_D 1·44028, n_F 1·44600, $n_{G'}$ 1·45027; R_C 42·39, R_D 42·59, R_F 43·07, $R_{G'}$ 43·43; Mn_D^{20} 201·97. Densities determined: d_4^{20} 0·8683, $d_4^{41\cdot6}$ 0·8520, $d_4^{61\cdot9}$ 0·8376, $d_4^{85\cdot9}$ 0·8182.

22·2°	5385	0·8666	1·0137	29·44	376·9	60·0°	4843	0·8384	1·0148	26·50	379·5
40·6	5079	0·8528	1·0143	27·79	377·5	84·0	4507	0·8196	1·0155	24·68	381·4
										Mean	378·8

645. β-n-*Hexylaminopropionitrile.* B. p. 126°/9 mm.; M 154·25; n_C 1·44084, n_D 1·44325, n_F 1·44888, $n_{G'}$ 1·45314; R_C 47·07, R_D 47·30, R_F 47·83, $R_{G'}$ 48·20; Mn_D^{20} 222·63. Densities determined: d_4^{20} 0·8651, $d_4^{40\cdot0}$ 0·8508, $d_4^{59\cdot7}$ 0·8366, $d_4^{86\cdot1}$ 0·8168.

18·4°	5483	0·8663	1·0135	29·97	416·6	61·0°	4885	0·8357	1·0146	26·73	419·7
40·0	5182	0·8508	1·0140	28·34	418·3	86·2	4564	0·8167	1·0153	24·99	422·2
										Mean	419·2

646. β-*Diethylaminopropionitrile.* B. p. 76°/11 mm.; M 126·20; n_C 1·43292, n_D 1·43540, n_F 1·44136, $n_{G'}$ 1·43540; R_C 37·87, R_D 38·06, R_F 38·52, $R_{G'}$ 38·85; Mn_D^{20} 181·15. Densities determined: d_4^{20} 0·8659, $d_4^{40\cdot5}$ 0·8492, $d_4^{60\cdot5}$ 0·8336, $d_4^{86\cdot7}$ 0·8116.

	H	d_4^t	γ	P	t	H	d_4^t	γ	P
17·1°	15·09	0·8683	30·51	341·6	60·9°	13·52	0·8333	26·23	342·7
20·9	14·93	0·8652	30·08	341·6	86·6	12·64	0·8117	23·89	343·7
40·5	14·25	0·8492	28·17	342·4				Mean	342·4

647. β-*Di*-n-*propylaminopropionitrile.* B. p. 105·5°/11 mm., M 154·25; n_C 1·43524, n_D 1·43771, n_F 1·44361, $n_{G'}$ 1·44800; R_C 47·05, R_D 47·28, R_F 47·84, $R_{G'}$ 48·25; Mn_D^{20} 221·77. Densities determined: d_4^{20} 0·8558, $d_4^{41\cdot5}$ 0·8392, $d_4^{61\cdot4}$ 0·8249, $d_4^{86\cdot5}$ 0·8055.

14·1°	14·74	0·8603	29·52	417·9	61·5°	13·26	0·8248	25·46	420·1
41·3	13·90	0·8394	27·16	419·5	87·3	12·47	0·8049	23·37	421·3
								Mean	419·7

648. β-*Di*-n-*butylaminopropionitrile*. B. p. 120°/10 mm.; M 182·31; n_C 1·44009, n_D 1·44255, n_F 1·44844, $n_{G'}$ 1·45292; R_C 56·33, R_D 56·60, R_F 57·25, $R_{G'}$ 57·74; Mn_D^{20} 263·00. Densities determined: d_4^{20} 0·8532, $d_4^{40\cdot9}$ 0·8380, $d_4^{59\cdot9}$ 0·8244, $d_4^{85\cdot8}$ 0·8063.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
19·9°	14·70	0·8533	29·20	496·7	60·6°	13·42	0·8239	25·74	498·4
40·5	14·07	0·8383	27·46	497·8	85·9	12·63	0·8062	23·71	499·0
								Mean	498·0

649. β-*Di*-n-*amylaminopropionitrile*. B. p. 149°/8 mm.; M 210·36; n_C 1·44342, n_D 1·44586, n_F 1·45178, $n_{G'}$ 1·45632; R_C 65·55, R_D 65·87, R_F 66·62, $R_{G'}$ 67·19; Mn_D^{20} 304·09. Densities determined; d_4^{20} 0·8515, $d_4^{41\cdot1}$ 0·8363, $d_4^{61\cdot3}$ 0·8226, $d_4^{86\cdot6}$ 0·8044.

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
21·0°	5238	0·8508	1·0139	28·64	572·0	60·2°	4701	0·8234	1·0149	25·73	575·4
39·5	4987	0·8374	1·0143	27·28	574·1	86·2	4338	0·8047	1·0158	23·77	577·2
										Mean	574·7

650. β-*Methoxypropionitrile*, B. p. 165·5°/759 mm.; M 85·11; n_C 1·40111, n_D 1·40317, n_F 1·40793, $n_{G'}$ 1·41260; R_C 22·01, R_D 22·11, R_F 22·34, $R_{G'}$ 22·58; Mn_D^{20} 119·43. Densities determined: d_4^{20} 0·9398, $d_4^{40\cdot6}$ 0·9209, $d_4^{60\cdot4}$ 0·9011, $d_4^{87\cdot0}$ 0·8763.

13·2°	6747	0·9464	1·0120	36·82	221·5	59·9°	5676	0·9016	1·0136	31·03	222·8
40·1	6106	0·9214	1·0129	33·35	222·0	86·0	5156	0·8773	1·0145	28·21	223·6
										Mean	222·5

651. β-*Ethoxypropionitrile*. B. p. 58°/10 mm.; M 99·13; n_C 1·40513, n_D 1·40751, n_F 1·41216, $n_{G'}$ 1·41651; R_C 26·67, R_D 26·81, R_F 27·08, $R_{G'}$ 27·33; Mn_D^{20} 139·53. Densities determined: d_4^{20} 0·9112, $d_4^{42\cdot0}$ 0·8913, $d_4^{59\cdot5}$ 0·8749, $d_4^{86\cdot5}$ 0·8512.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
19·6°	14·90	0·9116	31·62	257·9	61·6°	13·44	0·8730	27·32	259·6
41·2	14·14	0·8920	29·37	258·7	86·9	12·60	0·8508	24·96	259·0
								Mean	258·6

652. β-n-*Propoxypropionitrile*. B. p. 73·5°/10 mm.; M 113·16; n_C 1·41082, n_D 1·41306, n_F 1·41820, $n_{G'}$ 1·42232; R_C 31·32, R_D 31·47, R_F 31·82, $R_{G'}$ 32·09; Mn_D^{20} 159·91. Densities determined: d_4^{20} 0·8967, $d_4^{42\cdot4}$ 0·8772, $d_4^{62\cdot5}$ 0·8601, $d_4^{85\cdot7}$ 0·8391.

20·7°	14·57	0·8961	30·40	296·5	61·9°	13·20	0·8606	26·45	298·2
40·0	13·89	0·8793	28·44	297·2	84·5	12·52	0·8402	24·59	299·9
								Mean	298·0

653. β-n-*Butoxypropionitrile*. B. p. 91°/10 mm.; M 127·18; n_C 1·41607, n_D 1·41816, n_F 1·42317, $n_{G'}$ 1·42770; R_C 35·91, R_D 36·07, R_F 36·45, $R_{G'}$ 36·78; Mn_D^{20} 180·37. Densities determined: d_4^{20} 0·8890, $d_4^{39\cdot3}$ 0·8734, $d_4^{59\cdot7}$ 0·8570, $d_4^{85\cdot6}$ 0·8353.

14·9°	14·64	0·8930	30·44	334·5	61·6°	13·18	0·8553	26·24	336·6
19·9	14·40	0·8891	29·81	334·3	86·8	12·48	0·8343	24·24	338·2
40·2	13·87	0·8727	28·18	335·8				Mean	335·9

654. β-n-*Amyloxypropionitrile*. B. p. 117°/18 mm.; M 141·21; n_C 1·42225, n_D 1·42446, n_F 1·42961, $n_{G'}$ 1·43337; R_C 40·55, R_D 40·73, R_F 41·16, $R_{G'}$ 41·51; Mn_D^{20} 201·15. Densities determined: d_4^{20} 0·8856, $d_4^{40\cdot3}$ 0·8701, $d_4^{60\cdot8}$ 0·8541, $d_4^{86\cdot5}$ 0·8329.

t	Δp	d_4^t	ϕ	γ	P	t	Δp	d_4^t	ϕ	γ	P
15·6°	5624	0·8890	1·0135	30·74	374·1	60·2°	4906	0·8546	1·0149	26·85	376·2
40·5	5238	0·8699	1·0142	28·65	375·6	85·2	4538	0·8339	1·0157	24·86	378·1
										Mean	376·0

655. β-n-*Hexyloxypropionitrile*. B. p. 115·5°/9 mm.; M 155·24; n_C 1·42568, n_D 1·42787, n_F 1·43314, $n_{G'}$ 1·43726; R_C 45·20, R_D 45·41, R_F 45·89, $R_{G'}$ 46·28; Mn_D^{20} 221·67. Densities determined: d_4^{20} 0·8794, $d_4^{40\cdot0}$ 0·8646, $d_4^{60\cdot3}$ 0·8483, $d_4^{86\cdot1}$ 0·8284.

19·0°	5562	0·8802	1·0135	30·40	414·1	60·4°	4939	0·8482	1·0147	27·03	417·3
40·3	5248	0·8644	1·0141	28·70	415·7	85·8	4562	0·8286	1·0155	24·98	418·9
										Mean	416·5

656. *Ethyl azodiformate.* B. p. 104·5°/12 mm.; M 174·16; n_C 1·41921, n_D 1·42176, n_F and $n_{G'}$ could not be determined; R_C 39·54, R_D 39·89; Mn_D^{20} 247·67. Densities determined: d_4^{20} 1·1129, $d_4^{44·7}$ 1·0876, $d_4^{61·4}$ 1·0703, $d_4^{85·9}$ 1·0450.

t	H	d_4^t	γ	P	t	H	d_4^t	γ	P
22·1°	12·78	1·1107	33·05	376·0	61·7°	11·63	1·0700	28·97	377·6
42·1	12·22	1·0903	31·02	377·0	87·3	10·75	1·0437	26·12	377·2
								Mean	377·0

657. n-*Propyl azodiformate.* B. p. 122°/11 mm.; M 202·21; n_C 1·42459, n_D 1·42712; R_C 48·69, R_D 48·94; Mn_D^{20} 288·57. Densities determined: d_4^{20} 1·0610, $d_4^{49·9}$ 1·0418, $d_4^{60·2}$ 1·0234, $d_4^{86·5}$ 0·9978.

20·3°	13·07	1·0607	32·28	454·4	61·2°	11·75	1·0224	27·97	454·8
40·0	12·34	1·0418	29·93	454·0	87·6	10·94	0·9967	25·39	455·4
								Mean	454·7

658. n-*Butyl azodiformate.* B. p. 142°/11 mm.; M 230·26; n_C 1·43113, n_D 1·43370; R_C 57·58, R_D 57·88; Mn_D^{20} 330·12. Densities determined: d_4^{20} 1·0354, $d_4^{39·9}$ 1·0174, $d_4^{59·5}$ 1·0000, $d_4^{86·1}$ 0·9750.

16·8°	13·14	1·0383	31·76	529·5	60·0°	11·92	0·9995	27·74	528·8
40·1	12·41	1·0172	29·39	527·1	86·5	11·22	0·9752	25·47	530·5
								Mean	529·0

659. *Ethyl* n-*propyl carbonate.* B. p. 145·5°/760 mm.; M 132·16; n_C 1·39167, n_D 1·39357, n_F 1·39818, $n_{G'}$ 1·41043; R_C 32·87, R_D 33·01, R_F 33·36, $R_{G'}$ 33·59; Mn_D^{20} 184·18. Densities determined: d_4^{20} 0·9567, $d_4^{40·5}$ 0·9361, $d_4^{60·9}$ 0·9155, $d_4^{86·9}$ 0·8894.

16·9°	12·07	0·9598	26·97	313·8	61·9°	10·47	0·9145	22·29	314·0
21·9	11·87	0·9548	26·39	313·7	87·7	9·58	0·8877	19·84	314·0
41·0	11·25	0·9356	24·51	314·3				Mean	314·0

660. n-*Butyl ethyl carbonate.* B. p. 167°/759 mm.; M 146·18; n_C 1·39887, n_D 1·40082, n_F 1·40557, $n_{G'}$ 1·40886; R_C 37·51, R_D 37·67, R_F 38·07, $R_{G'}$ 38·34; Mn_D^{20} 204·77. Densities determined: d_4^{20} 0·9424, $d_4^{40·9}$ 0·9235, $d_4^{61·5}$ 0·9034, $d_4^{85·3}$ 0·8806.

18·8°	12·26	0·9435	26·93	352·9	61·4°	10·76	0·9035	22·69	352·9
40·9	11·49	0·9235	24·70	352·9	86·2	9·99	0·8797	20·46	353·4
								Mean	353·0

661. n-*Amyl ethyl carbonate.* B. p. 188°/760 mm.; M 160·21; n_C 1·40572, n_D 1·40771, n_F 1·41259, $n_{G'}$ 1·41598; R_C 42·14, R_D 42·34, R_F 42·79, $R_{G'}$ 43·10; Mn_D^{20} 225·53. Densities determined: d_4^{20} 0·9329, $d_4^{40·0}$ 0·9157, $d_4^{59·5}$ 0·8977, $d_4^{85·1}$ 0·8756.

23·9°	12·34	0·9295	26·70	391·8	60·7°	11·10	0·8966	23·17	392·0
40·7	11·76	0·9151	25·06	391·7	87·0	10·19	0·8739	20·73	391·1
								Mean	391·7

662. *Ethyl* n-*hexyl carbonate.* B. p. 206·5°/764 mm.; M 174·23; n_C 1·41093, n_D 1·41296, n_F 1·41784, $n_{G'}$ 1·42132; R_C 46·76, R_D 46·97, R_F 47·45, $R_{G'}$ 47·80; Mn_D^{20} 246·19. Densities determined: d_4^{20} 0·9250, $d_4^{40·2}$ 0·9070, $d_4^{60·1}$ 0·8892, $d_4^{86·1}$ 0·8663.

16·1°	13·01	0·9285	28·12	432·1	60·5°	11·48	0·8888	23·75	432·7
40·4	12·12	0·9068	25·59	432·1	87·1	10·57	0·8654	21·30	432·5
								Mean	432·4

663. n-*Butyl* n-*propyl carbonate.* B. p. 187°/764 mm.; M 160·21; n_C 1·40514, n_D 1·40711, n_F 1·41195, $n_{G'}$ 1·41527; R_C 42·12, R_D 42·30, R_F 42·75, $R_{G'}$ 43·05; Mn_D^{20} 225·43. Densities determined: d_4^{20} 0·9325, $d_4^{40·6}$ 0·9133, $d_4^{60·0}$ 0·8959, $d_4^{85·9}$ 0·8714.

16·1°	12·54	0·9361	27·33	391·3	61·0	11·04	0·8950	23·00	392·0
20·1	12·42	0·9324	26·96	391·5	86·7	10·21	0·8707	20·70	392·5
40·9	11·75	0·9130	24·92	392·3				Mean	391·9

664. *Di*-n-*amyl carbonate.* B. p. 238·5°/757 mm.; M 202·29; n_C 1·41847, n_D 1·42056, n_F 1·42561, $n_{G'}$ 1·42923; R_C 55·94, R_D 56·18, R_F 56·77, $R_{G'}$ 57·19; Mn_D^{20} 287·37. Densities determined: d_4^{20} 0·9123, $d_4^{40\cdot5}$ 0·8949, $d_4^{61\cdot0}$ 0·8788, $d_4^{86\cdot5}$ 0·8574.

t	H	d_4'	γ	P	t	H	d_4'	γ	P
19·9°	13·10	0·9124	27·83	509·2	60·7°	11·66	0·8790	23·86	508·6
40·4	12·37	0·8950	25·77	509·3	86·7	10·96	0·8572	21·87	510·3
								Mean	509·4

665. *Di*-n-*hexyl carbonate.* B. p. 146·5°/9 mm.; M 230·34; n_C 1·42519, n_D 1·42727, n_F 1·43252, $n_{G'}$ 1·43619; R_C 65·40, R_D 65·69, R_F 66·38, $R_{G'}$ 66·85; Mn_D^{20} 328·77. Densities determined: d_4^{20} 0·9009, $d_4^{41\cdot0}$ 0·8850, $d_4^{61\cdot5}$ 0·8692, $d_4^{86\cdot6}$ 0·8501.

t	Δp	d_4'	ϕ	γ	P	t	Δp	d_4'	ϕ	γ	P
18·0°	5151	0·9024	1·0149	28·19	588·2	60·2°	4491	0·8702	1·0165	24·62	589·6
40·0	4821	0·8858	1·0157	26·41	589·5	86·0	4086	0·8498	1·0177	22·43	589·8
										Mean	589·3

666. n-*Heptyl cyanide.* B. p. 82·5°/10 mm.; M 125·21; n_C 1·41838, n_D 1·42056, n_F 1·42569, $n_{G'}$ 1·42935; R_C 38·79, R_D 38·97, R_F 39·38, $R_{G'}$ 39·68; Mn_D^{20} 177·88. Densities determined: d_4^{20} 0·8141, $d_4^{40\cdot4}$ 0·7985, $d_4^{60\cdot0}$ 0·7838, $d_4^{86\cdot5}$ 0·7630.

22·5°	5099	0·8122	1·0136	27·87	354·2	61·0°	4521	0·7830	1·0148	24·74	356·7
40·3	4805	0·7986	1·0142	26·28	355·0	86·1	4147	0·7633	1·0157	22·72	358·1
										Mean	356·0

667. n-*Octyl cyanide.* B. p. 100°/11 mm.; M 139·24; n_C 1·42356, n_D 1·42576, n_F 1·43088, $n_{G'}$ 1·43472; R_C 43·49, R_D 43·68, R_F 44·14, $R_{G'}$ 44·48; Mn_D^{20} 198·53. Densities determined: d_4^{20} 0·8164, $d_4^{41\cdot0}$ 0·8016, $d_4^{61\cdot7}$ 0·7866, $d_4^{85\cdot9}$ 0·7691.

23·1°	5206	0·8142	1·1033	28·21	395·0	61·0°	4584	0·7871	1·0146	25·08	395·9
40·2	4927	0·8022	1·0139	26·94	395·4	85·8	4227	0·7692	1·0155	23·15	397·0
										Mean	395·8

414. n-*Hexyl cyanide.* The sample of XVII, **414** was redistilled and the surface tensions determined by the method of maximum bubble pressure. Unlike those obtained by the capillary-rise method, the results were constant and reproducible.

19·1°	5117	0·8107	1·0135	27·97	316·1	61·2°	4384	0·7787	1·0152	24·00	316·0
40·0	4740	0·7949	1·0143	25·93	315·6	86·5	4050	0·7584	1·0160	22·19	318·2
										Mean	316·5

668. *Acrylonitrile.* A commercial sample (Light) was carefully fractionated. B. p. 76·5°/748 mm.; M 53·06; n_C 1·38836, n_D 1·39142, n_F 1·39890, $n_{G'}$ 1·40478; R_C 15·54, R_D 15·64, R_F 15·91, $R_{G'}$ 16·12; Mn_D^{20} 73·83. Densities determined: d_4^{20} 0·8064, $d_4^{41\cdot0}$ 0·7839.

t	H	d_4'	γ	P	t	H	d_4'	γ	P
15·1°	14·70	0·8117	27·76	150·1	40·6°	13·58	0·7843	24·80	151·1
17·8	14·62	0·8088	27·53	150·3				Mean	150·5

669. *Benzene.* "AnalaR" benzene was frozen twice and then twice distilled through a Widmer column. B. p. 80·2°/769 mm.; M 78·108; n_C 1·49622, n_D 1·50089, n_F 1·51298, $n_{G'}$ 1·52306; R_C 25·973, R_D 26·181, R_F 26·715, $R_{G'}$ 27·155; Mn_D^{20} 117·23; d_4^{20} 0·8788. $n_{G'}$ was determined with the Hilger–Chance refractometer since the value was outside the range of the Pulfrich refractometer.

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99. *The Kinetics of Chlorohydrin Formation. Part III.* The Reaction between Hypochlorous Acid and Crotonic Acid at Constant* pH.

By D. A. Craw and G. C. Israel.

The kinetics of the reaction between hypochlorous acid solutions and solutions containing such concentrations of crotonic acid and crotonate ion as to yield a constant pH 4·73 have been investigated at 25·00° ± 0·01°. The reaction velocity conforms to the expression

$$v = k_2^{I}[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + (k_2^{II} + k_3^{II}[R{\cdot}CO_2H])[HOCl]^2$$

where R = $CH_3{\cdot}CH{:}CH{\cdot}$. k_2^{II} and k_3^{II} are interpreted as being the specific rates of formation of chlorine monoxide from hypochlorous acid, the latter being the specific rate of formation catalysed by crotonic acid. The value of k_2^{II} (4·0) for this reaction was found to be only half that (8·2) reported in Part II of this series for the reaction between hypochlorous acid and allyl alcohol at the same pH. No explanation of this discrepancy has as yet been found.

The kinetics of addition of hypochlorous acid to crotonic acid were studied by Schilov and Kaniaev (*J. Phys. Chem. U.S.S.R.*, 1934, **5**, 654; *Trans. Inst. Chem. Tech. Ivanovo*, 1935, 19) who were unable to derive a definite kinetic equation to express the rate of the reaction. These workers observed that the reaction velocity was approximately proportional to the concentration of crotonic acid, increased as the pH increased, and was not affected by the presence of neutral salts. For relatively high concentrations of crotonic acid, the reaction velocity was found to be approximately proportional to the concentration of hypochlorous acid, but for relatively low concentrations of crotonic acid the reaction velocity varied approximately as the square of the hypochlorous acid concentration.

In view of the results obtained by Israel, Martin, and Soper (*J.*, 1950, 1282) and Israel (*ibid.*, p. 1286) for the kinetics of addition of hypochlorous acid to allyl alcohol, the reaction between hypochlorous acid and crotonic acid has been reinvestigated in solutions of pH 4·73. Since hypochlorous acid reacts with both un-ionised crotonic acid and crotonate ion, the ratio of the concentrations of these two species was kept throughout at $[R{\cdot}CO_2^-]/[R{\cdot}CO_2H] = 1{\cdot}096$ (R = $CH_3{\cdot}CH{:}CH{\cdot}$). This served the purpose of maintaining the reacting solutions at a pH close to 4·73 (Vogel and Jeffery, *Chem. and Ind.*, 1937, 600; Ives, Linstead, and Riley, *J.*, 1933, 561) and thus avoiding catalytic effects caused by addition of a buffer such as acetate–acetic acid solutions (cf. Israel, *J.*, 1950, 1286).

In view of the probable complexity of the kinetic equation, the initial velocity, v_0, was determined in each experiment by the method described previously (Israel, Martin, and Soper, *loc. cit.*). In each case the pH of the reaction mixture was determined seven minutes after the commencement of the reaction. The results are summarised in Table 1.

From the results obtained by Schilov and Kaniaev (*locc. cit.*), it seemed likely that the kinetic equation would contain two terms, *viz.*, $k_2^{I}[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])$ and $k_3^{II}[HOCl]^2[R{\cdot}CO_2H]$, the latter being assumed to be dependent on the concentration of un-ionised crotonic acid and not on the concentration of crotonate ion, by analogy with the results obtained by Israel (*J.*, 1950, 1286) for the reaction between hypochlorous acid and allyl alcohol in the presence of acetate–acetic acid buffers. Thus, for constant concentrations of hypochlorous acid, the kinetic equation was assumed to be of the form, $v_0 = k_1[R{\cdot}CO_2H]_0 + v_{res.}$, since in all experiments the ratio $[R{\cdot}CO_2^-]/[R{\cdot}CO_2H]$ was constant and equal to 1·096. That the values of $v_0^{obs.}$ vary linearly with $[R{\cdot}CO_2H]_0$ is clear from Fig. 1 in which five of the seven series of experimental values have been plotted. In each case the best line was located by the method of least squares and the values of k_1 and $v_{res.}$ so obtained are given in Table 2.

* Part II, *J.*, 1950, 1286.

That the residual velocity, $v_{res.}$, varies as the square of the concentration of hypochlorous acid, *i.e.*, is equal to $k_2^{II}[HOCl]^2$, is clear from Fig. 2, the best line being located by the method of least squares. The slope of this line gives $k_2^{II} = 4{\cdot}0$ l. mole^{-1} min.$^{-1}$.

TABLE 1. $[R{\cdot}CO_2^-] = 1{\cdot}096[R{\cdot}CO_2H]$. *Initial* pH = 4·73. *Temp.* = 25·00° ± 0·01°.

$10^3[HOCl]_0$ (mole l.$^{-1}$)	$10^3([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])_0$ (mole l.$^{-1}$)	pH (after 7 min.)	$10^5 v_0$ (mole l.$^{-1}$ min.$^{-1}$) (obs.)	$10^5 v_0$ (mole l.$^{-1}$ min.$^{-1}$) (calc.)	$10^3[HOCl]_0$ (mole l.$^{-1}$)	$10^3([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])_0$ (mole l.$^{-1}$)	pH (after 7 min.)	$10^3 v_0$ (mole l.$^{-1}$ min.$^{-1}$) (obs.)	$10^3 v_0$ (mole l.$^{-1}$ min.$^{-1}$) (calc.)
1·00	2·0	4·60	1·6	1·5	3·10	2·0	4·52	8·0	8·6
0·99	4·0	4·65	2·6	2·6	3·11	4·0	4·63	13·4	13·3
0·99	6·0	4·69	3·6	3·7	3·09	8·0	4·67	22·1	22·5
0·99	8·0	4·69	4·8	4·7	3·08	10·0	4·70	27·0	27·0
0·99	10·0	4·65	5·8	5·8	3·08	12·0	4·70	30·4	31·6
0·99	12·0	4·65	7·1	6·9					
					3·90	2·0	4·44	13·0	12·6
1·90	2·0	4·68	3·8	3·9	3·90	4·0	4·54	19·5	19·1
1·89	4·0	4·71	6·0	6·3	3·91	8·0	4·54	34·1	32·2
1·90	8·0	4·70	11·3	11·1	3·90	10·0	4·58	40·6	38·6
1·89	10·0	4·69	13·6	13·5	3·90	12·0	4·60	47·2	45·0
1·89	12·0	4·69	15·8	15·8					
					4·33	2·0	4·06	14·6	15·1
2·96	2·0	4·50	7·9	7·9	4·30	4·0	4·18	22·2	22·4
2·96	4·0	4·55	12·8	12·3	4·31	8·0	4·30	36·9	37·6
2·96	8·0	4·57	21·4	21·0	4·30	10·0	4·33	44·3	45·0
2·95	10·0	4·59	25·8	25·3	4·29	12·0	4·40	50·8	52·3
2·95	12·0	4·57	30·4	29·7					
3·01	2·0	—	8·4	8·1					
3·00	4·0	—	12·5	12·6					
2·97	8·0	—	20·8	21·2					
3·00	10·0	—	25·6	25·9					
2·97	12·0	—	30·0	30·2					

TABLE 2.

$10^3[HOCl]_0$ (mean) (mole l.$^{-1}$)	0·99	1·89	2·95	2·99	3·09	3·90	4·30
$10^2 k_1$ (min.$^{-1}$)	1·15	2·56	4·67	4·53	4·72	7·24	7·65
$10^5 v_{res.}$ (mole l.$^{-1}$ min.$^{-1}$)	0·42	1·32	3·60	3·89	3·98	6·00	7·46

The variation of the values of k_1 with the concentration of hypochlorous acid is given by

$$k_1 = 2{\cdot}096k_2^I[HOCl]_0 + k_3^{II}[HOCl]_0^2$$

or

$$k_1/[HOCl]_0 = 2{\cdot}096k_2^I + k_3^{II}[HOCl]_0$$

as may be seen from Fig. 3 in which $k_1/[HOCl]_0$ has been plotted as ordinates against $[HOCl]_0$ as abscissæ. The best line through these points was determined by the method of least squares and in this way the values of the two constants were found to be $k_2^I = 4{\cdot}5$ l. mole^{-1} min.$^{-1}$ and $k_3^{II} = 2{\cdot}1 \times 10^3$ l.^{2} mole^{-2} min.$^{-2}$.

Thus the complete kinetic equation is shown to be :

$$v = k_2^I[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + (k_2^{II} + k_3^{II}[R{\cdot}CO_2H])[HOCl]^2 \quad . \quad . \quad (i)$$

or, by substitution of the values obtained for the three constants :

$$v = 4{\cdot}5[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-]) + (4{\cdot}0 + 2{\cdot}1 \times 10^3[R{\cdot}CO_2H])[HOCl]^2 \quad (ii)$$

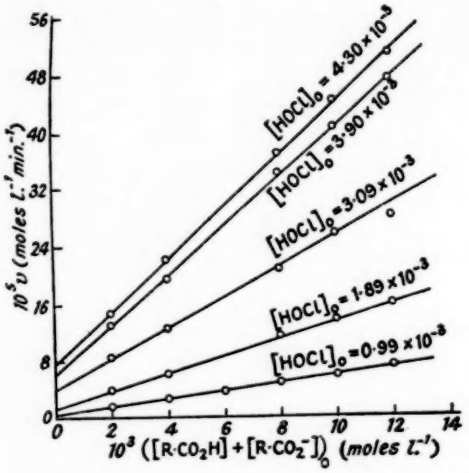
That equation (ii) gives a reasonably accurate interpretation of the course of the reaction, is confirmed since values of v_0 calculated by using it are in good agreement with the observed values (see Table 1).

The term $k_2^I[HOCl]([R{\cdot}CO_2H] + [R{\cdot}CO_2^-])$ in equation (i) is probably complex, and represents the rate of addition of hypochlorous acid to un-ionised crotonic acid, and to crotonate ion, and possibly also includes a term for the rate of formation of crotonyl hypochlorite (R·CO·OCl) from crotonic acid and hypochlorous acid (cf. Israel, *loc. cit.*).

However, the value of k_2^I is constant, since, in this investigation, the ratio of the concentrations of crotonate ion and crotonic acid was constant.

The second term $k_2^{II}[HOCl]^2$ probably represents the rate of formation of chlorine monoxide in solution by the reaction $2HOCl \longrightarrow Cl_2O + H_2O$. However, the value of

FIG. 1.



k_2^{II} (4·0) for this reaction is distinctly lower than that obtained previously (8·2) for the reaction between allyl alcohol and hypochlorous acid (Israel, *loc. cit.*). A possible cause for the discrepancy may be found in the qualities of the hypochlorous acid used in the two investigations, since Ourisson and Kastner (Congr. Chim. ind., Compt. rend. XVIII Congr., Sept. 1938, p. 983) have reported that mercuric oxide is appreciably soluble in hypochlorous acid solutions. Since the solutions employed in the earlier work were stored

FIG. 2.

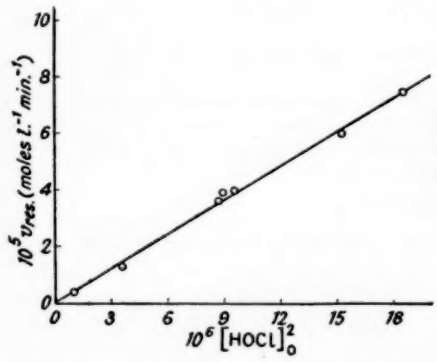
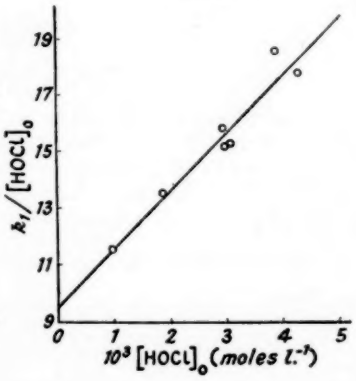


FIG. 3.



over yellow mercuric oxide, appreciable quantities of mercuric hypochlorite would certainly be present therein. In the present investigation, mercury-free solutions of hypochlorous acid were used throughout.

Again, as may be seen from Table 1, the pH of each reaction mixture was found to be rather less than the calculated value, an effect due partly to the hypochlorous acid added and partly to the presence of chlorohydroxybutyric acids and their salts. The lower pH

of the various reaction mixtures would result in somewhat different values of the specific rate constants (cf. Schilov and Kaniaev, *loc. cit.*).

The final term $k_3^{II}[HOCl]^2[R{\cdot}CO_2H]$ in the kinetic equation may be interpreted as the rate of formation of chlorine monoxide from hypochlorous acid under the catalytic influence of un-ionised crotonic acid, it being assumed that crotonate ion is inactive in this respect (cf. Israel, *loc. cit.*). The value of k_3^{II} found is of the same order as that found by Israel for the catalytic effect of un-ionised acetic acid, a result which would be expected since crotonic acid and acetic acid are acids of approximately the same strength.

Experimental

Materials.—In this investigation, crotonic acid, from B.D.H., was recrystallised from light petroleum; it had m. p. 72°.

Hypochlorous acid was prepared by a method similar to that used by Israel, Martin, and Soper (*loc. cit.*) except that the distillate was not stored over mercuric oxide. Instead, it was treated with bismuth hydroxide, filtered, and stored in the dark at *ca.* 6°. Hypochlorous acid solutions were prepared from these stock solutions immediately before use by shaking them with a small amount of bismuth hydroxide, filtering them quickly, and diluting them to the required strength with distilled water. Such solutions gave negative tests for Bi^{+++} (cf. Vogel, "Qualitative Chemical Analysis," 3rd edn., Longmans, 1945, p. 152). In cases where hypochlorous acid had been stored over yellow mercuric oxide, appreciable amounts of mercuric ions were found in solution (cf. Ourisson and Kastner, *loc. cit.*).

Kinetic Measurements.—These were carried out by the method described previously (Israel, Martin, and Soper, *loc. cit.*).

pH *Measurements.*—A Leeds–Northrup pH meter was used for this purpose.

The authors acknowledge the helpful advice and criticisms offered by Professor F. G. Soper, University of Otago, Dunedin, N.Z. One of them (D. A. C.) acknowledges the award by the University of Tasmania of a Commonwealth Research Studentship.

University of Tasmania, Hobart. [*Received, July 18th,* 1951.]

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100. *Ring–Chain Tautomerism in the Acid Halides of the Half-esters of Dibasic Acids.*

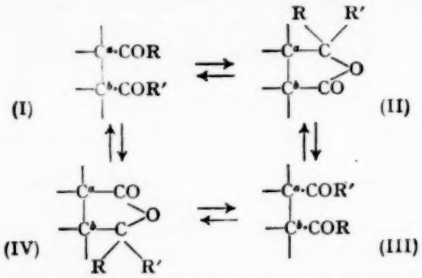
By B. H. Chase and D. H. Hey.

A study has been made of the formation of ester acid chlorides derived from 1-methyl hydrogen 4-nitrophthalate, 1-methyl and 2-methyl hydrogen 3-nitrophthalate, and the acid methyl esters of αα-diphenyl-succinic and -glutaric acids. By an investigation of the products of various reactions of these ester acid chlorides, partial rearrangement has been shown to occur in all cases, giving rise to derivatives of the isomeric ester acid chloride formed by interchange of the ester and acid chloride groups. A number of analogous cases in the literature have been discussed, and a mechanism for the reaction proposed. Some confusion in the literature concerning the structure of certain compounds obtained by methods involving ester acid chlorides has been resolved.

The existence of ring–chain tautomerism in the diacid halides of certain dibasic acids is well established. The diacid chlorides of phthalic acid and of succinic acid, for example, exhibit typical tautomeric properties which are represented by the equilibrium between the two structures (I) and (II), where R and R′ are Cl. The occurrence of similar tautomeric properties in the acid chlorides of the half-esters of dibasic acids, *e.g.*, (I) $\rightleftarrows$ (II), where R is OAlk and R′ is Cl, has not hitherto been generally recognised, although there is considerable experimental evidence which can only be interpreted satisfactorily on the basis of the existence of such tautomeric forms.

Systems in which R and R′ are not identical differ from those of the diacid chlorides

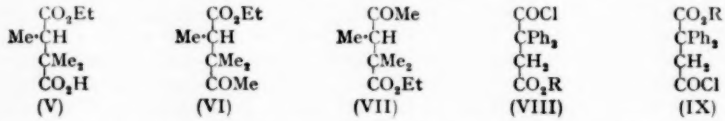
of dibasic acids in that, provided the molecule of the parent dicarboxylic acid is itself dissymmetric by the possession of some structural feature which will differentiate the atoms C^a and C^b, the cyclic tautomeride (II) now allows ring fission to occur with formation of a second open-chain form (III). This in turn leads to a second ring form (IV), which completes the cycle. The experimental proof of existence of the two tautomerides (I)



and (II) in the acid chlorides of dibasic acids depends largely on evidence obtained from the chemical reactions of these two forms which lead to fundamentally different structures, but in the series of the acid chlorides of the half-esters it is possible to utilise the reactions of the isomeric open-chain forms (I) and (III). Failure to recognise the existence of this type of tautomerism has led in the past to much confusion, and a number of reactions in which such half-ester acid chlorides have been used require reinvestigation. Any investigation of such reactions, however, depends in the first instance on the availability of reliable methods for the preparation of the isomeric half-esters (I and III; R = OAlk, R′ = OH) of unambiguous constitution. Much of the confusion on the subject in the literature can be traced to the use of half-esters of doubtful identity.

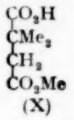
The existence of ring–chain tautomerism in the systems under discussion requires that the two carboxyl groups in the parent acid should be in close spatial proximity so that a stable ring can be formed. Examples of this phenomenon are therefore to be sought in the aliphatic series in derivatives of succinic, glutaric, and adipic acids and in the aromatic series in derivatives of *o*-dicarboxylic acids.

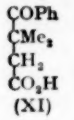
1 : 2-*Dicarboxylic Acid Series.*—In the succinic acid series Bardhan (*J.*, 1928, 2604) obtained both ethyl αββ-trimethyl-lævulate (VI) and ethyl ααβ-trimethyl-lævulate (VII) from the action of methylzinc iodide on the acid chloride of the β-ethyl ester (V) of ααβ-trimethylsuccinic acid. The concomitant formation of the two isomeric esters (VI) and (VII) from the half-ester (V) can be explained by the existence of the cyclic tautomeric

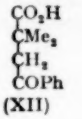


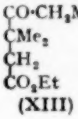
system represented by the forms (I), (II), (III), and (IV). Bardhan, however, attributed the formation of the second keto-ester to the presence of the isomeric half-ester in his starting material. On the other hand, Anschütz and Drugman (*Ber.*, 1897, **30**, 2651) have reported the conversion of the acid chlorides of the two isomeric half-esters of mesaconic acid into the corresponding ester-anilides and ester-*p*-toluidides but record the formation of one product only in each case. In this instance the *trans*-relationship of the two carboxyl groups precludes the formation of a cyclic tautomeride. Anschütz (*Annalen*, 1907, **354**, 117) also carried out a Friedel–Crafts reaction between benzene and each of the isomeric acid chloride half-esters of phenylsuccinic acid and again reported the formation of a single ketonic product in each case. Salmon-Legagneur and Soudan (*Compt. rend.*, 1944, **218**, 681), however, state that the acid chlorides (VIII; R = alkyl) of the β-alkyl esters of αα-diphenylsuccinic acid readily rearrange to those of the α-alkyl esters (IX) during the course of preparation by the action of thionyl chloride on the

(β-)half ester. They further claim that such rearrangement can be avoided by treatment of the dry silver salt of the acid ester with thionyl chloride in cold ethereal solution. After reaction between the acid chloride prepared from the β-methyl ester (X) of αα-dimethylsuccinic acid and benzene in the presence of aluminium chloride Rothstein and Saboor (*J.*, **1943**, **427**) isolated, not the expected β-benzoyl-β-methylbutyric acid (XI), but the

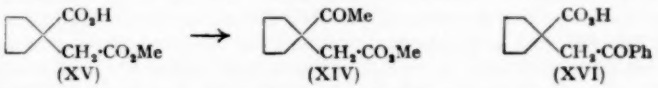

(X)


(XI)


(XII)

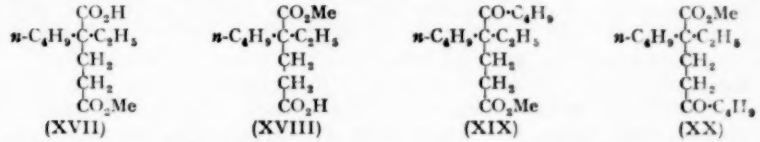

(XIII)

isomeric β-benzoyl-αα-dimethylpropionic acid (XII), whereas Rosambo (*Ann. Chim.*, **1923**, **19**, 335), using the acid chloride of the (β-)ethyl ester of the same acid and ethylzinc iodide, obtained ethyl ββγ-trimethyl-lævulate (XIII). Bardhan (*J.*, 1928, 2593) has reported the formation of methyl 1-acetyl*cyclo*pentylacetate (XIV) by the action of

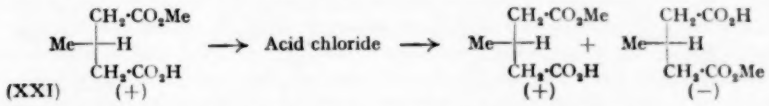

(XV) (XIV) (XVI)

methylzinc chloride on the acid chloride from the half-ester (XV), but, when Sen-Gupta (*J. Indian Chem. Soc.*, **1934**, **11**, 392) used the same ester acid chloride in a Friedel–Crafts reaction with benzene, he obtained a ketone which has since been shown (Saboor, *J.*, **1945**, 923) to be 1-phenacyl*cyclo*pentane-1-carboxylic acid (XVI) which yields a lactone, and not the expected 1-benzoyl*cyclo*pentylacetic acid. The work of Blaise (*Bull. Soc. chim.*, **1899**, **21**, 715) and of Haworth and King (*J.*, **1914**, **105**, 1348) on the ester acid chlorides of αα-dimethylsuccinic acid contains no indication of rearrangement, but the half-esters used by these workers were of uncertain identity. A further example of the rearrangement in this series has recently been provided by Turner, Bhattacharyya, Graber, and Johnson (*J. Amer. Chem. Soc.*, **1950**, **72**, 5654) in their improved synthesis of bisdehydrodoisynolic acid.

1 : 3-*Dicarboxylic Acid Series.*—In the glutaric acid series Cason (*J. Org. Chem.*, 1948, **13**, 227) has reported that when the isomeric half-esters (XVII) and (XVIII) of α-*n*-butyl-α-ethylglutaric acid are each converted into their acid chlorides by means of thionyl chloride and then treated with 2 : 4 : 6-tribromoaniline in boiling xylene, the same anilide is obtained in low yield in each case. It was inferred that a mixture of the two isomeric ester acid chlorides had been obtained in both cases but that only that from the unhindered carboxylic acid had reacted with the base. Confirmatory evidence for this hypothesis was obtained from the action of di-*n*-butylcadmium on the two acid chlorides, which gave in each case a mixture of the isomeric keto-esters (XIX) and (XX). Ställberg-Stenhagen


(XVII) (XVIII) (XIX) (XX)

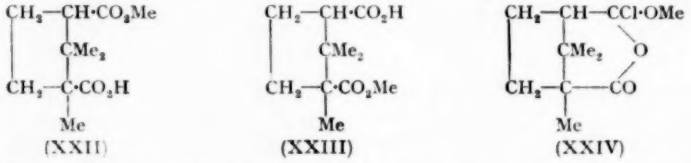
(*J. Amer. Chem. Soc.*, **1947**, **69**, 2568) has reported that when an optically active methyl hydrogen β-methylglutarate (XXI) is converted into the acid chloride by means of thionyl chloride and then recovered by hydrolysis racemisation takes place. Racemisation can



(XXI) (+) (+) (−)

be avoided, however, by the use of oxalyl chloride in benzene solution, or of *pure* thionyl chloride at temperatures below 30°. It is inferred that the use of less pure thionyl chloride

or of higher temperatures leads to rearrangement and, hence, racemisation. Ställberg-Stenhagen suggests that rearrangement occurs through the formation of the anhydride. It may be noted that Cason (*loc. cit.*) was able to reduce the extent of his rearrangement but was not able to eliminate it entirely by the use of low temperatures and purified thionyl chloride. Qudrat-i-Khuda (*J.*, 1930, 206) has suggested that the *ortho*- and *allo*-methyl hydrogen camphorates, which had previously been assigned the structures (XXII) and (XXIII) respectively, were in fact stereoisomerides. This conclusion was based



largely on the claim that the acid chloride of either ester gave (*a*) the same keto-ester on treatment with methylzinc iodide and (*b*) only the *allo*-ester on hydrolysis. Bredt (*J. pr. Chem.*, 1932, **133**, 89), however, maintained that the two compounds were structural isomerides, which could undergo rearrangement through the chloro-methoxy-lactone (XXIV), a view which was later confirmed by Salmon-Legagneur (*Bull. Soc. Sci. Bretagne*, 1938, **15**, 189), who showed that each half-ester could be converted into a mixture of both through the acid chloride. The difficulties experienced by Haller and Blanc (*Compt. rend.*, 1905, **141**, 697) in the preparation of the anilides and *p*-toluidides of the *ortho*- and *allo*-camphoric acids must be attributed to the existence of this rearrangement.

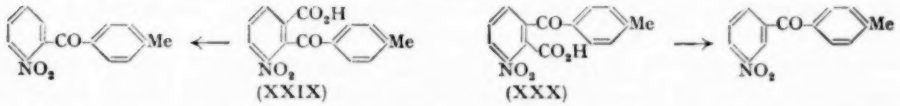
The reactions of ester acid chlorides in the 1 : 2- and more particularly the 1 : 3-dicarboxylic acid series have frequently been used in synthetic work in the steroid field for converting an acid ester into the next higher homologue by the Arndt–Eistert method (Litvan and Robinson, *J.*, 1938, 1997; Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 834 and subsequent papers). In none of the many examples recorded has any evidence of rearrangement been reported and in many cases the yields of the required product are high. This may be attributed to the wide use made of oxalyl chloride, in place of thionyl chloride or phosphorus pentachloride, for the preparation of the acid chloride, or to the use of purified thionyl chloride under mild experimental conditions (cf. Ställberg-Stenhagen, *loc. cit.*). On the other hand, when unpurified thionyl chloride or phosphorus pentachloride has been used, low yields and difficulties in purification have sometimes been reported (cf. Litvan and Robinson, *loc. cit.*; Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1940, **62**, 901; etc.).

1 : 4-*Dicarboxylic Acid Series.*—In the adipic acid series no examples of rearrangement have so far come to light. No reference to rearrangement was reported by Palfray (*Ann. Chim.*, 1923, **20**, 331), who prepared the phenyl ester of homocamphoric acid by the action of sodium phenoxide on the acid chloride. Litvan and Robinson (*loc. cit.*) obtained hydrocamphorylacetic acid in 53% yield by means of an Arndt–Eistert reaction on the half-ester of homocamphoric acid and recorded no evidence of rearrangement.

o-*Dicarboxylic Acids.*—Several examples of rearrangement have been recorded with the acid chlorides of half-esters in the aromatic series. Hayashi, Turuoka, Morikawa, and Namikawa (*Bull. Chem. Soc. Japan*, 1936, **11**, 191) reported the reaction of the acid chloride from 1-methyl hydrogen 3-nitrophthalate (XXV) on benzene in the presence of aluminium chloride and obtained after hydrolysis an acid, m. p. 236—237°, which they regarded as 6-nitrobenzophenone-2-carboxylic acid (XXVI). The acid chloride pre-

pared from the isomeric half-ester (XXVII) on similar treatment gave an acid, m. p. 160—161°, regarded as 3-nitrobenzophenone-2-carboxylic acid (XXVIII), together with

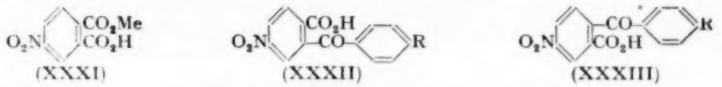
a small quantity of the higher-melting isomeric acid (XXVI), the formation of which they ascribed to the rearrangement of the acid chloride. These results, however, were in direct contrast to the earlier work of Lawrance (*J. Amer. Chem. Soc.*, 1920, **42**, 1875) who, using the corresponding isomeric 1- and 2-ethyl hydrogen 3-nitrophthalates, obtained nitrobenzophenonecarboxylic acids melting at 157—160° and 220—221°, respectively. Lawrance (*ibid.*, 1921, **43**, 2578) also submitted the acid chlorides from both 1- and 2-ethyl hydrogen 3-nitrophthalates to a Friedel–Crafts reaction with toluene and obtained from the former an acid, m. p. 123—126°, regarded as 4′-methyl-6-nitrobenzophenone-2-carboxylic acid (XXIX) and from the latter an acid, m. p. 262—265°, regarded as the isomeric 4′-methyl-3-nitrobenzophenone-2-carboxylic acid (XXX). Later, Mitter and



(XXIX) (XXX)

Sarkar (*J. Indian Chem. Soc.*, 1930, **7**, 619) obtained an acid claimed to be 4′-methyl-6-nitrobenzophenone-2-carboxylic acid, m. p. 218—219°, by the condensation of 3-nitrophthalic anhydride with toluene in the presence of aluminium chloride. More recently, Blicke and Otsuki (*J. Amer. Chem. Soc.*, 1941, **63**, 1945) have prepared a range of 1-alkyl 2-dialkylaminoalkyl 3-nitrophthalates by reactions involving ester acid chlorides, but no reference is made to any rearrangements.

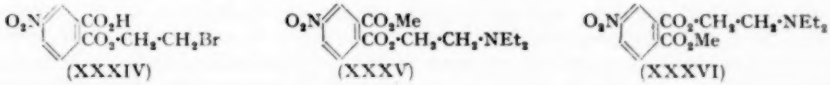
Hayashi and Nakayama (*J. Soc. Chem. Ind. Japan*, 1933, **36**, 203B) also submitted the acid chloride derived from 1-methyl hydrogen 4-nitrophthalate (XXXI) to a Friedel–Crafts reaction with chlorobenzene and obtained both 4′-chloro-5-nitrobenzophenone-2-carboxylic acid (XXXII; R = Cl) and 4′-chloro-4-nitrobenzophenone-2-carboxylic acid (XXXIII; R = Cl). By means of a Friedel–Crafts reaction between 4-nitrophthalic anhydride and toluene, Lawrance (*J. Amer. Chem. Soc.*, 1921, **43**, 2579) obtained an acid, m. p. 100—105°, which was also obtained from the acid chloride from 1-methyl hydrogen 4-nitrophthalate (XXXI) and toluene and was therefore regarded as 4′-methyl-5-nitrobenzophenone-2-carboxylic acid (XXXII; R = Me). Repetition of Lawrance's work on the anhydride of 4-nitrophthalic acid and toluene by Mitter and Sarkar (*loc. cit.*) gave



(XXXI) (XXXII) (XXXIII)

a methylnitrobenzophenonecarboxylic acid, m. p. 170—171°. The same reaction in the hands of Hayashi and Nakayama (*J. Soc. Chem. Ind. Japan*, 1934, **37**, 238B) gave an acid, m. p. 217—218°, together with a second acid, m. p. 190—191°, regarded as 4′-methyl-4-nitrobenzophenone-2-carboxylic acid (XXXIII; R = Me).

An unambiguous example of rearrangement in the 4-nitrophthalic acid series is provided by the work of Blicke and Castro (*J. Amer. Chem. Soc.*, 1941, **63**, 2437), who attempted to convert 1-2′-bromoethyl hydrogen 4-nitrophthalate (XXXIV) by means of its acid chloride into 1-2′-diethylaminoethyl 2-methyl 4-nitrophthalate (XXXV) but



(XXXIV) (XXXV) (XXXVI)

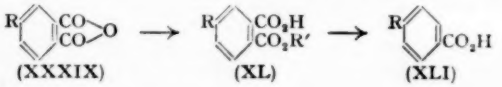
obtained instead the isomeric 2-2′-diethylaminoethyl 1-methyl 4-nitrophthalate (XXXVI), identical with the product obtained directly from 1-methyl hydrogen 4-nitrophthalate and 2-diethylaminoethyl chloride. Similar results were obtained with the ethyl, propyl, *iso*propyl, and *iso*butyl esters, and the authors concluded that they had obtained 2-2′-bromoethyl hydrogen 4-nitrophthalate and not the corresponding 1-ester in the initial reaction between 2-bromoethyl alcohol and 4-nitrophthalic anhydride. This, however, is contrary to the normal course followed in the reactions of 4-nitrophthalic anhydride,

as shown in the work of Wegscheider *et al.* (*Monatsh.*, 1903, **24**, 805; 1905, **26**, 1093) as well as in that of Blicke and Castro themselves. It seems highly probable that the anomalous stage resides not in the formation of the acid ester from the anhydride but rather in the formation and behaviour of the ester acid chloride. A further example of rearrangement in the 4-nitrophthalic acid series has been provided by Hey and Walker (*J.*, 1948, 2214), who showed that treatment of the acid chloride derived from 1-methyl hydrogen 4-nitrophthalate (XXXI) with alkaline hydrogen peroxide gave two isomeric peroxides, which on decomposition in boiling benzene solution yielded methyl 4- and 5-nitrodiphenyl-2-carboxylate, (XXXVIII) and (XXXVII) respectively.

(XXXVII) (XXXVIII)

Hayashi, Turuoka, Morikawa, and Namikawa (*Bull. Chem. Soc. Japan*, 1936, **11**, 184) have reported the preparation of the acid chlorides of 1-methyl hydrogen 3-methylphthalate and of 2-methyl hydrogen 4-methylphthalate and their reaction with benzene in the presence of aluminium chloride. The formation of one ketonic acid only was reported in each reaction, on the structure of which the constitutions of the original half-esters were based. Friedel–Crafts reactions have been reported by Kirpal (*Monatsh.*, 1909, **30**, 355; 1910, **31**, 295) and Halla (*ibid.*, 1911, **32**, 747) on the acid chloride of the isomeric half-esters of cinchomeronic and quinolinic acids and no example of rearrangement has been recorded. The experimental detail is, however, sparse and unambiguous proof of the constitutions of the products is lacking.

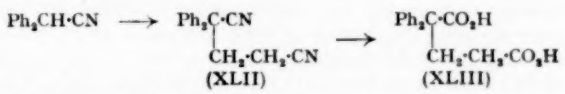
Preparation of Half-esters.—The following methods have been used for the preparation of half-esters of unambiguous constitution. 1-Methyl hydrogen 3-nitrophthalate, 2-methyl hydrogen 3-nitrophthalate, and 1-methyl hydrogen 4-nitrophthalate were prepared by established methods, but a new route was developed for 2-methyl hydrogen 4-nitrophthalate. Nitration of *o*-toluic acid by van Scherpenzeel's method (*Rec. Trav. chim.*, 1901, **20**, 173) gave a mixture of nitrotoluic acids from which by esterification and fractional crystallisation methyl 2-methyl-5-nitrobenzoate was obtained. Oxidation of the latter with neutral potassium permanganate gave 2-methyl hydrogen 4-nitrophthalate. An attempt was made to prepare 2-methyl hydrogen 4-aminophthalate by the hydrogenolysis of 1-benzyl 2-methyl 4-nitrophthalate, but the action of benzyl alcohol on 4-nitrophthalic anhydride (XXXIX; R = NO_2) appeared to give a mixture of the


(XXXIX) (XL) (XLI)

two isomeric monobenzyl esters, from which on fractional crystallisation only the pure 1-benzyl ester (XL; R = NO_2, R′ = Ph·CH_2) was obtained in low yield. The constitution of this ester was established by decarboxylation with copper chromite, followed by hydrolysis, which gave *p*-nitrobenzoic acid (XLI; R = NO_2). Treatment of 4-chlorophthalic anhydride (XXXIX; R = Cl) with methyl alcohol also appeared to give a mixture of the two isomeric half-esters, from which only the 1-methyl ester (XL; R = Cl, R′ = Me) could be isolated in pure form. Dry distillation of the silver salt, followed by hydrolysis, gave *p*-chlorobenzoic acid (XLI; R = Cl). 1-Methyl hydrogen 4-nitro*iso*phthalate was obtained by esterification of 4-nitro*iso*phthalic acid prepared by the oxidation of 4-nitro-*m*-xylene, and 4-methyl hydrogen 2-nitroterephthalate was similarly obtained in good yield by the oxidation of 2-nitro-*p*-xylene and subsequent esterification (cf. Noyes, *Amer. Chem. J.*, 1888, **10**, 482).

αα-Diphenylsuccinic acid was prepared by Salmon-Legagneur's method (*Compt. rend.*, 1939, **208**, 1507) from diphenylacetonitrile. The Fischer–Speier esterification of the acid gave a mixture of the β-ester and the diester. Partial hydrolysis of the latter gave the α-ester. A much improved method has been developed for the preparation of the homologous αα-diphenylglutaric acid (XLIII). Condensation of diphenylacetonitrile

with acrylonitrile gave αα-diphenylglutarodinitrile (XLII) in excellent yield, which on hydrolysis gave the acid (XLIII):

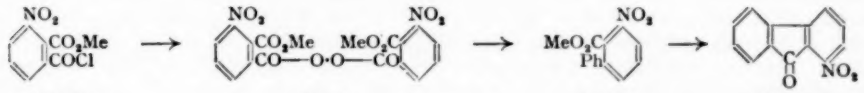


(XLII) (XLIII)

Following the previous example, Fischer–Speier esterification now gave a mixture of the γ-methyl ester and the diester, which on partial hydrolysis gave the α-methyl ester (cf. Salmon-Legagneur, *Compt. rend.*, 1941, **213**, 182).

Reactions of Half-esters.—In order to detect any rearrangement in the acid chlorides of the half-esters of dibasic acids described above, the most suitable reactions in the aromatic series were found to be (*a*) the formation of peroxides followed by their decomposition in boiling benzene solution, and (*b*) the formation of aromatic ketonic acids by means of Friedel–Crafts reactions with benzene or toluene. In the latter method the presence of *o*-nitro-groups is disadvantageous (see Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," 1941, pp. 252, 255), and aliphatic tertiary acid chlorides tend to react abnormally in giving rise to the elimination of carbon monoxide. In the aliphatic series reactions with a secondary base such as methylaniline or diethylamine can be used.

3-Nitrophthalic Acid Series.—Attempts to prepare a peroxide from 1-methyl hydrogen 3-nitrophthalate failed but the isomeric 2-methyl ester (cf. XLIV), by use of phosphorus pentachloride or pure thionyl chloride followed by alkaline hydrogen peroxide, gave the peroxide (XLV) in almost quantitative yield. Decomposition of the peroxide in boiling benzene solution gave a mixture of 2-methyl hydrogen 3-nitrophthalate (cf. XLIV) and methyl 3-nitrodiphenyl-2-carboxylate (XLVI). Hydrolysis of the latter to the free acid and treatment with concentrated sulphuric acid gave the hitherto unknown 1-nitrofluorenone (XLVII), which was reduced and acetylated to give 1-acetamidofluorenone, identical with the product obtained by the Hofmann degradation of the amide of fluorenone-1-carboxylic acid (Huntress, Pfister, and Pfister, *J. Amer. Chem. Soc.*, 1942, **64**, 2847) followed by acetylation. The high yields obtained in the preparation of this peroxide and its reaction with benzene, coupled with the absence of any isomeric compounds, shows that little rearrangement, if any, can have taken place. The possibility of limited rearrangement cannot be entirely excluded, since it is known that the isomeric acid chloride does not appear to form a peroxide.



(XLIV) (XLV) (XLVI) (XLVII)

The action of the acid chloride derived from 1-methyl hydrogen 3-nitrophthalate on benzene in the presence of aluminium chloride yielded an oily product in only 16% yield, which on hydrolysis gave two crystalline isomeric keto-acids, m. p.s 161·5—162·5° and 236—237°. In a similar reaction using the acid chloride derived from 2-methyl hydrogen 3-nitrophthalate the product, obtained in 75% yield, was mainly a methyl ester, m. p. 94·5°, which on hydrolysis gave the lower-melting acid obtained from 1-methyl hydrogen 3-nitrophthalate, while hydrolysis of the ester contained in the mother-liquors gave a small quantity of the higher-melting acid. The lower-melting acid gave 3-nitrobenzophenone on decarboxylation and must therefore be 3-nitrobenzophenone-2-carboxylic acid (XXVIII). The higher-melting acid must be 6-nitrobenzophenone-2-carboxylic acid (XXVI). The relationship of these results to those of previous workers is shown by the m. p.s in Table 1.

The constitutions assigned to these keto-acids by Hayashi *et al.* were based on those of the acid esters used and these are now shown to be in agreement with the results obtained on decarboxylation. The constitutions assigned by Lawrance, however, who

isolated only one acid in each case, are reversed, and it is difficult to give any logical reason for this confusion, since the work of Bogert and Boroschek (*J. Amer. Chem. Soc.*, 1901, **23**, 746), to which reference is made for the original half-esters used, is clear and unequivocal. Lawrance also showed that the higher-melting keto-acid gave *o*-nitrobenzoic acid on alkaline fusion, whereas the lower-melting acid gave *m*-nitrobenzoic acid, but no reliable inference can be drawn from these observations. In the light of the results now presented, the structures assigned by Lawrance must be reversed both for the two nitrobenzophenone-carboxylic acids and for the two aminobenzophenone-carboxylic acids which he obtained from them.

TABLE 1.

Starting ester	Benzophenone-2-carboxylic acid : 6-nitro-	3-nitro-	Starting ester	Benzophenone-2-carboxylic acid : 6-nitro-	3-nitro-
1-Ethyl (*a*)	157—160° (decomp.)	None	2-Ethyl (*a*) ...	None	220—221° (decomp.)
1-Methyl (*b*) ...	236—237	None	2-Methyl (*b*) ...	236—237°	160—161 (main)
1-Methyl (*c*) ...	236—237	161·5—162·5°	2-Methyl (*c*) ...	236—238	162·5—163·5 (main)

(*a*) Lawrance, *J. Amer. Chem. Soc.*, 1920, **42**, 1875. (*b*) Hayashi, Turuoka, Morikawa, and Namikawa, *Bull. Chem. Soc. Japan*, 1936, **11**, 191. (*c*) This paper.

The action of the acid chloride prepared from 1-methyl hydrogen 3-nitrophthalate on toluene in the presence of aluminium chloride gave a mixture of esters consisting largely of the methyl ester of 4′-methyl-6-nitrobenzophenone-2-carboxylic acid. Hydrolysis of the ester gave the free acid (XXIX), m. p. 219·5—220·5°, the structure of which was proved by decarboxylation to give 4′-methyl-2-nitrobenzophenone. Fractional crystallisation of the mother-liquors gave a second ester in very small yield, which gave an acid, m. p. 211—212°. This acid and its methyl ester on admixture depressed the melting points of both 4′-methyl-6- and -3-nitrobenzophenone-2-carboxylic acid and their methyl esters respectively. This acid must therefore be regarded as a derivative of 2′- or 3′-methylbenzophenone. The presence of the isomeric 4′-methyl-3-nitrobenzophenone-2-carboxylic acid (XXX) was not detected in the reaction product. In a similar reaction with 2-methyl hydrogen 3-nitrophthalate the resulting mixture of esters consisted largely of the methyl ester of 4′-methyl-3-nitrobenzophenone-2-carboxylic acid, hydrolysis of which gave the free acid, m. p. 188—189° (XXX), which was smoothly decarboxylated to 4′-methyl-3-nitrobenzophenone. No other isomeride was isolated. It seems likely, by analogy with the results of the corresponding reactions with benzene, that in both of these reactions with toluene some rearrangement has occurred but the isolation of the rearranged product was rendered difficult owing to the presence of additional isomerides, which arise from reactions at the *ortho*- and *meta*-positions with regard to the methyl group. There is considerable confusion in the literature with regard to the methylnitrobenzophenone-carboxylic acids, and Table 2 shows by the m. p.s that the present results are in agreement with those of Mitter and Sarkar for the one isomer prepared by them and are in total disagreement with those of Lawrance.

TABLE 2.

Starting compound	4′-Methylbenzophenone-2-carboxylic acid : 6-nitro-	3-nitro-	Starting compound	4′-Methylbenzophenone-2-carboxylic acid : 6-nitro-	3-nitro-
Anhydride (*a*) ...	122—126° *	262—265° *	Anhydride (*b*) ...	218—219° †	None
1-Ethyl ester (*a*)...	123—126° *	None	1-Methyl ester (*c*)	219·5—220·5° ‡	None isolated
2-Ethyl ester (*a*)	None	262—265° *	2-Methyl ester (*c*)	None isolated	188—189°

(*a*) Lawrance, *J. Amer. Chem. Soc.*, 1921, **43**, 2578. (*b*) Mitter and Sarkar, *J. Indian Chem. Soc.* 1930, **7**, 619. (*c*) This paper.

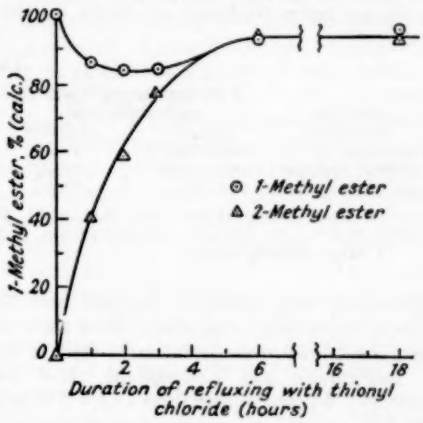
* With decomp. † Yellow. ‡ Colourless.

Experiments were also carried out on the preparation of the phenyl esters of 1-methyl and of 2-methyl hydrogen 3-nitrophthalate by means of the acid chlorides. The former half-ester gave largely 1-methyl 2-phenyl 3-nitrophthalate and the latter largely 2-methyl 1-phenyl 3-nitrophthalate, which confirms the fact that in this series little rearrangement

appears to have taken place. There was, however, qualitative evidence of some rearrangement, and an attempt was therefore made to determine whether an equilibrium is set up by utilising the different rates of esterification of the two isomeric half-esters.

A weighed quantity of each acid ester was converted into the acid chloride under standard conditions, "crude" thionyl chloride being used in order to favour rearrangement. After rapid removal of the excess of thionyl chloride, the product was hydrolysed with aqueous sodium hydrogen carbonate, and the mixture of half-esters recovered. The determination of the composition of the product was effected by means of esterification with methyl alcohol and sulphuric acid under standard conditions. The esterification of the sterically hindered 1-methyl ester under these conditions gave only 7·2% of the neutral dimethyl ester, whereas the less hindered 2-methyl ester gave 93·7% of the neutral dimethyl ester. It thus follows that a mixture of half-esters will give a value for the percentage unesterified between 92·8 and 6·3%. On the not unreasonable assumption that the presence of one isomeride does not substantially affect the rate of esterification of the other, the composition of any mixture of half-esters can be determined from the percentage of unesterified material by simple proportion using the known values for the pure esters.

Isomerisation of the acid chlorides of the two methyl hydrogen 3-nitrophthalates.



The acid chlorides from 1-methyl and 2-methyl hydrogen 3-nitrophthalate were prepared with five different times of refluxing and the products were treated as described above. The results, expressed in the figure, show that the acid chloride of the 1-methyl ester has undergone maximum rearrangement after 2 hours' refluxing and approaches a steady value at about 96% of 1-methyl ester on prolonged heating. The 2-methyl ester approaches asymptotically the same value. This phenomenon is probably due to the formation of the diacid chloride on prolonged heating, which on hydrolysis to the diacid would simulate the behaviour of the 1-methyl ester, which it yields on esterification. The formation of this diacid chloride prevents the realisation of a true equilibrium between the two isomeric acid chlorides.

4-Nitrophthalic Acid Series.—Reactions in the 4-nitrophthalic acid series were confined to those of the more accessible 1-methyl ester. The acid chloride, prepared with purified thionyl chloride, was converted into the peroxide, as described by Hey and Walker (*loc. cit.*), the decomposition of which in boiling benzene gave a mixture of the methyl esters of 5- and 4-nitrodiphenyl-2-carboxylic acid (XXXVII) and (XXXVIII). Hydrolysis and subsequent ring closure with concentrated sulphuric acid gave both 3- and 2-nitrofluorenone. Rearrangement had thus taken place, and similar results were obtained when phosphorus pentachloride was used in place of thionyl chloride. These results are therefore similar to those previously reported by Hey and Walker (*loc. cit.*), who used unpurified thionyl chloride. When the same acid chloride (prepared with phosphorus pentachloride) was allowed to react with benzene in the presence of aluminium chloride the product consisted largely of methyl 4-nitrobenzophenone-2-carboxylate, the product of rearrangement, with a smaller quantity of the methyl ester of 5-nitrobenzophenone-2-carboxylic acid. Hydrolysis gave the corresponding acids (XXXIII; R = H) and (XXXII; R = H). These experiments show the existence of appreciable rearrangement which was not eliminated even by the use of purified thionyl chloride and by working at temperatures below 30° both in the preparation of the acid chloride and in the subsequent reaction with benzene. This result is in contrast to the experience of Ställberg-Stenhagen (*loc. cit.*) with the half-esters of β-methylglutaric acid. In the Friedel–Crafts reaction,

however, the possibility of rearrangement after the addition of the aluminium chloride cannot be excluded.

Analogous results were obtained in the reaction between the acid chloride from 1-methyl hydrogen 4-nitrophthalate (prepared with purified thionyl chloride) and toluene in the presence of aluminium chloride, which gave a mixture of esters from which both 4′-methyl-4-nitrobenzophenone-2-carboxylic acid (XXXIII; R = Me) and 4′-methyl-5-nitrobenzophenone-2-carboxylic acid (XXXII; R = Me) were obtained on hydrolysis. The former acid gave 4′-methyl-4-nitrobenzophenone on decarboxylation, whereas the latter gave 4′-methyl-3-nitrobenzophenone. The reports in the literature concerning these acids are again confused, as shown by the m. p.s in Table 3. The present results are in

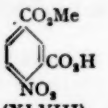
TABLE 3.

Starting compound	4′-Methylbenzophenone-2-carboxylic acid: 5-nitro-	4-nitro-	Starting compound	4′-Methylbenzophenone-2-carboxylic acid: 5-nitro-	4-nitro-
Anhydride (*a*) ...	100—105° *	Trace	Anhydride (*c*) ...	217—218°	190—191°
1-Methyl ester (*a*)	101—105 *	None	1-Methyl ester (*d*)	217·5—218·5	192—193
Anhydride (*b*)	170—171	Trace			

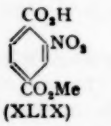
(*a*) Lawrance, *J. Amer. Chem. Soc.*, 1921, **43**, 2579. (*b*) Mitter and Sarkar, *J. Indian Chem. Soc.*, 1930, **7**, 619. (*c*) Hayashi and Nakayama, *J. Soc. Chem. Ind. Japan*, 1934, **37**, 238. (*d*) This paper.
* With decomposition.

agreement with those of Hayashi and Nakayama. The acid obtained by Mitter and Sarkar is probably a mixture, since their amino-acid obtained on reduction was converted into the known 6-methylalizarin (Mitter and Biswas, *J. Indian Chem. Soc.*, 1928, **5**, 775).

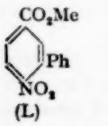
iso*Phthalic and Terephthalic Acid Series.*—Reactions carried out with 1-methyl hydrogen 4-nitro*iso*phthalate (XLVIII) and with 4-methyl hydrogen 2-nitroterephthalate (XLIX) showed no evidence of rearrangement. Thus, the acid chloride prepared from 1-methyl hydrogen 4-nitro*iso*phthalate on treatment with aniline gave only one product, presumably the anilide of 1-methyl hydrogen 4-nitro*iso*phthalate. Conversion of the same acid chloride into the peroxide and decomposition of the latter in boiling benzene gave only methyl 6-nitrodiphenyl-3-carboxylate (L), which on hydrolysis and decarboxylation gave 2-nitrodiphenyl. In similar manner the acid chloride prepared from 4-methyl hydrogen 2-nitroterephthalate gave a peroxide, which underwent decomposition in boiling benzene to give methyl 2-nitrodiphenyl-4-carboxylate (LI). The free acid was obtained on hydrolysis.



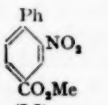
(XLVIII)



(XLIX)



(L)

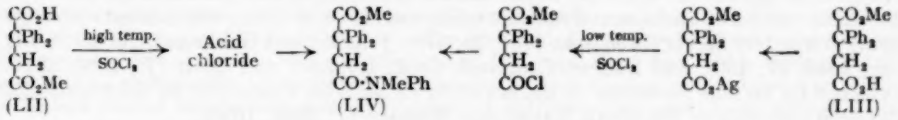


(LI)

Succinic and Glutaric Acid Series.—Reactions were restricted to the methyl esters of αα-diphenyl-succinic and -glutaric acids.

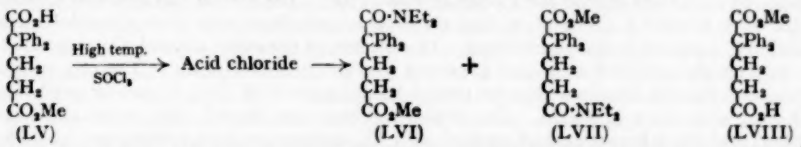
When the acid chloride prepared from the β-methyl ester (LII) of αα-diphenylsuccinic acid was treated with aniline the only product isolated was αα*N*-triphenylsuccinimide, probably formed during recrystallisation (cf. Salmon-Legagneur and Soudan, *loc. cit.*). When the aniline was replaced by methylaniline, in order to exclude the possibility of cyclisation, two products were obtained, namely, the methyl ester of an *N*-methyl-αα-diphenylsuccinanilide, m. p. 150—150·5°, and the bis-(*N*-methylanilide), m. p. 156°. In order to ascertain the exact structure of the former, recourse was had to the silver salt technique of Salmon-Legagneur and Soudan (*loc. cit.*), who showed that when ester acid chlorides are prepared by the action of thionyl chloride at low temperatures on the dry silver salt of the half-ester, the resulting ester acid chloride has the expected structure and rearrangement is entirely suppressed. When the α-methyl ester of αα-diphenylsuccinic acid (LIII) was converted in this manner into the acid chloride and then treated with methylaniline, two products were obtained, namely, an ester *N*-methylanilide, m. p.

150° (LIV), identical with the compound prepared as described above from the β-methyl ester, and an unidentified neutral compound, m. p. 166—167°.



The application of the silver salt technique to the β-methyl ester (LII) of αα-diphenylsuccinic acid led only to inconclusive results, presumably owing to steric hindrance in the acid chloride. The formation of the same ester-anilide (LIV) by these two routes indicated that rearrangement must occur in one of them. In agreement with Salmon-Legagneur and Soudan, it seems most likely that rearrangement occurs in the high-temperature reaction with thionyl chloride. The absence of a second isomeric ester-anilide from the high-temperature reaction does not exclude the possibility of the existence of a mixture of the two acid chlorides, since the β-ester α-acid chloride is sterically hindered.

In similar manner, when the γ-methyl ester of αα-diphenylglutaric acid (LV) was converted into the acid chloride with hot thionyl chloride and then treated with diethylamine, two isomeric ester diethylamides, (LVI) and (LVII), were obtained. When the silver salt of the α-methyl ester (LVIII) of αα-diphenylglutaric acid was treated with cold thionyl chloride and then with diethylamine, one ester diethylamide only was obtained which was identical with one of the diethylamides prepared by the former method and which presumably has the structure of the α-methyl ester (LVII) of *NN*-diethyl-αα-diphenylglutaramide. The application of the silver salt technique to the γ-methyl ester again led to inconclusive results, presumably owing to the reluctance of the hindered acid chloride to react with the secondary base. These results again indicate that rearrangement occurred when the γ-ester was treated with hot thionyl chloride.



Mechanism of the Rearrangement.—The absence of the evidence of the occurrence of any rearrangement with the acid chlorides of the half-esters of substituted *iso*phthalic and terephthalic acids suggests that the change is intramolecular rather than intermolecular and involves a cyclic intermediate. It is possible to visualise three types of intermediate, namely, (*a*) the anhydride of the dicarboxylic acid, (*b*) an oxonium chloride (LIX), and (*c*) an alkoxy-chloro-lactone (LX). Ställberg-Stenhagen (*loc. cit.*) regards the anhydride

as the essential intermediate in her reactions with derivatives of β-methylglutaric acid, but this suggestion cannot be applied to the reactions of 1-methyl hydrogen 4-nitrophthalate which yield mainly derivatives of 2-methyl hydrogen 4-nitrophthalate. The action of methanol on 4-nitrophthalic anhydride is known to lead almost quantitatively to the formation of the 1-methyl ester (Wegscheider and Lipschitz, *Monatsh.*, 1900, **21**, 805). An oxonium salt has been suggested by Prelog and Heimbach-Juhasz (*Ber.*, 1941, **74**, 1702) as an intermediate in the closely related isomerisation of γ-ethoxybutyryl and δ-ethoxyvaleryl chlorides to ethyl γ-chlorobutyrate and ethyl δ-chlorovalerate respectively. The lactone intermediate has been suggested by Bredt (*loc. cit.*), Salmon-Legagneur (*Bull. Soc. Sci. Bretagne*, 1938, **15**, 189), and Hayashi, Turuoka, and Nakayama (*J. Chem. Soc.*

Japan, 1935, **56**, 1096) for the reactions of specific half-ester halides, and the results now reported would appear to support the view that this mechanism is general. Such a theory is in agreement with the better-known examples of the tautomerism shown by the diacid halides of phthalic and succinic acids, and also with the closely related rearrangements studied by Meyer (*Monatsh.*, 1904, **25**, 477), Johnson and Goldman (*J. Amer. Chem. Soc.*, 1945, **67**, 430), and Badger, Campbell, Cook, Raphael, and Scott (*J.*, 1950, 2326). Evidence for lactone formation in the action of alcohols on *o*-dicarboxylic anhydrides has also been provided by Hirshberg, Lavie, and Bergman (*J.*, 1951, 1030).

Experimental

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of Half-esters.

1-Methyl hydrogen 3-nitrophthalate, m. p. 163·5—164°, was prepared in 71% yield by the method of Cohen, Woodroffe, and Anderson (*J.*, 1916, **109**, 222). 2-Methyl hydrogen 3-nitrophthalate, m. p. 152·5—153·5°, was prepared in 67% yield by the method of Dickinson, Crosson, and Copenhaver (*J. Amer. Chem. Soc.*, 1937, **59**, 1094). 1-Methyl hydrogen 4-nitrophthalate, m. p. 131·5—132·5°, was obtained in 93% yield as described by Wegscheider and Lipschitz (*Monatsh.*, 1900, **21**, 805).

1-*Benzyl Hydrogen* 4-*Nitrophthalate*.—4-Nitrophthalican hydride (16·4 g.) was boiled under reflux for 1 hour with benzyl alcohol (10·0 g.) in dry benzene (50 c.c.). After removal of the solvent under reduced pressure, the residue was taken up in ether (50 c.c.) and extracted with 5% aqueous sodium carbonate. Acidification of the alkaline extracts precipitated the crude half-ester as a pale yellow oil, which solidified at 0° (23·6 g.; m. p. 90—120°). Repeated crystallisation from benzene–light petroleum (b. p. 80—100°) gave 1-*benzyl hydrogen* 4-*nitrophthalate* in white prisms, m. p. 142—143·5° (Found: C, 59·6; H, 4·0. $C_{15}H_{11}O_6N$ requires C, 59·8, H, 3·7%). No pure isomeric acid ester could be obtained by fractional crystallisation of the filtrates. A portion of the acid ester (1·8 g.), copper chromite (1·8 g.), and redistilled quinoline (10 c.c.) were stirred for 1 hour at 160—170°. The cooled mixture was diluted with ether (20 c.c.), filtered from catalyst, and thoroughly extracted with 5N-hydrochloric acid and then with 5% aqueous sodium carbonate. Distillation of the ether yielded a brown oil (1·8 g.), which only partly solidified at 0° and appeared to contain nitrobenzene. The oily residue was boiled under reflux for 2 hours with a mixture of glacial acetic acid (6 c.c.), concentrated sulphuric acid (3 c.c.), and water (1·5 c.c.). The cooled solution was diluted with water and extracted with ether, and the ethereal extract washed with 5% aqueous sodium carbonate. Acidification of the alkaline extract, ether-extraction, and distillation of the ether gave *p*-nitrobenzoic acid (0·3 g.). Three recrystallisations from water yielded the pure acid, m. p. 235—237°, undepressed on admixture with an authentic specimen.

2-*Methyl Hydrogen* 4-*Nitrophthalate*.—Methyl 2-methyl-5-nitrobenzoate (5·0 g.) [prepared by nitration of *o*-toluic acid and subsequent esterification as described by van Scherpenzeel (*Rec. Trav. chim.*, 1901, **20**, 173)], potassium permanganate (12·5 g.), magnesium sulphate (5·3 g.), and water (250 c.c.) were vigorously stirred at 80—90° for 3 hours. The hot mixture was filtered at the pump, the residue was washed with hot water (100 c.c.), and the combined aqueous solutions were cooled and extracted with ether. Evaporation of the ethereal solution yielded unchanged ester (1·4 g.). Acidification of the alkaline solution and ether-extraction gave the crude 2-methyl ester (2·1 g.), m. p. 129—135°, raised on recrystallisation from benzene and subsequently from water to 141·5—143·5°. Wegscheider, Kusy, and Dubrav (*Monatsh.*, 1903, **24**, 827) recorded m. p. 140—142°.

1-*Methyl Hydrogen* 4-*Chlorophthalate*.—4-Chlorophthalic anhydride (16·0 g.) in absolute methanol (20 c.c.) was boiled under reflux for ½ hour. Removal of the methanol under reduced pressure yielded a colourless oil (18·7 g.), which solidified to a sticky white solid when kept. Five recrystallisations from benzene–light petroleum (b. p. 80—100°) gave 1-methyl hydrogen 4-chlorophthalate in colourless needles, m. p. 104—105° (Found: C, 50·7; H, 3·2. Calc. for $C_9H_7O_4Cl$: C, 50·4; N, 3·3%). Hayashi, Furusawa, and Turuoka [*J. Soc. Chem. Ind., Japan*, 1941, **44**, No. 11, 436B (Supp. Bdg.)] quote m. p. 107·5°. A portion of the acid ester (2·0 g.) was converted into the silver salt (2·7 g., 90%), and the latter dry-distilled at 40 mm. On the bath-temp. being raised to 250° a colourless oil (1·0 g.) distilled. The distillate, after being kept for 12 hours in 5% sodium hydrogen carbonate (2 c.c.) to remove any anhydride, was recovered by ether-extraction and boiled under reflux for 2 hours with a solution of potassium

hydroxide (1·0 g.) in 40% aqueous alcohol (15 c.c.). The cooled solution was diluted with water (20 c.c.), extracted with ether, and acidified. The crude precipitate (0·6 g.; m. p. 175—200°) on sublimation and recrystallisation from dilute acetic acid yielded *p*-chlorobenzoic acid, m. p. 232—235°, raised to 238—241° on admixture with an authentic specimen, m. p. 239—241°.

1-*Methyl Hydrogen* 4-*Nitroisophthalate*.—The addition of *m*-xylene to fuming nitric acid at 0° (Harmsen, *Ber.*, 1880, **13**, 1558; Holleman and Huisinger, *Rec. Trav. chim.*, 1908, **27**, 267) gave rise to considerable quantities of undesirable polynitro-compounds. Inversion of the procedure proved satisfactory and only traces of polynitro-compounds were formed. The reaction product was distilled with steam, the first fraction consisting of *m*-xylene ($d < 1$) being rejected, and then redistilled under reduced pressure; the product had b. p. 142—148°/48 mm. (yield 58%). Crude 4-nitro*iso*phthalic acid from the oxidation of 4-nitro-*m*-xylene (Axer, *Monatsh.*, 1920, **41**, 159) was esterified with methanol–sulphuric acid. The acidic product separated from benzene in colourless prisms (45%), m. p. 153·5° (Axer, *loc. cit.*, gives m. p. 154°).

4-*Methyl Hydrogen* 2-*Nitroterephthalate*.—2-Nitro-*p*-xylene (99·5 g.) and water (4 l.) were vigorously stirred at 80—90°, and potassium permanganate (469 g.) added in 8 portions during 3 hours. Stirring and heating were continued for a further 5 hours, the solution decolorised with sodium hydrogen sulphite and filtered, and the residue washed with hot water (1 l.). The combined aqueous solutions were concentrated to 500 c.c., acidified, and cooled to 0°, and the crude 2-nitroterephthalic acid was filtered off. Ether-extraction of the filtrates gave a further quantity of acid. The total yield was 104 g., m. p. 260° (cf. Noyes, *Amer. Chem. J.*, 1888, **10**, 485). The crude acid, on esterification with methanol–sulphuric acid, gave a neutral fraction (36 g.) which yielded dimethyl 2-nitroterephthalate (18·0 g.; m. p. 71·5°), and an acidic fraction, which yielded 4-methyl hydrogen 2-nitroterephthalate (56 g.; m. p. 134·5—136°). Wegscheider (*Monatsh.*, 1902, **23**, 407) records m. p. 73—74° and m. p. 133·5—135°, respectively.

The α- *and the* β-*Methyl Ester of* αα-*Diphenylsuccinic Acid*.—αα-Diphenylacetonitrile (Robb and Schultz, *Org. Synth.*, **28**, 55) was converted into ethyl β-cyano-ββ-diphenylpropionate (69%; m. p. 104—105°) by Salmon-Legagneur's method (*Compt. rend.*, 1939, **208**, 1507). Hydrolysis with aqueous-alcoholic potassium hydroxide and subsequently with concentrated hydrochloric acid–acetic acid yielded αα-diphenylsuccinic acid (75%), m. p. 169—170°. Salmon-Legagneur (*loc. cit.*) gives m. p. 197—199° with softening at 170°, but does not record a yield. Dry hydrogen chloride was passed for 2½ hours into a solution of αα-diphenylsuccinic acid (23·8 g.) in absolute methanol (60 c.c.) gently boiling under reflux. The majority of the excess of alcohol was then removed under reduced pressure, and the cooled residue taken up in ether. Extraction of the ether with excess of 10% aqueous sodium carbonate and acidification of the alkaline extract precipitated the β-methyl ester as a colourless oil, which solidified (15·3 g.) and was dried at 100°. Recrystallisation from benzene–light petroleum (b. p. 80—100°) gave β-methyl hydrogen αα-diphenylsuccinate in colourless prisms, m. p. 140·5—142°. Salmon-Legagneur (*loc. cit.*) records m. p. 141—143°, but no yield. Distillation of the ether from the neutral fraction (see above) gave dimethyl αα-diphenylsuccinate (9·9 g.) as a white crystalline solid, m. p. 85·5—88°. A sample crystallised from light petroleum (b. p. 80—100°) in rosettes of prisms, m. p. 86—88·5°. Salmon-Legagneur (*loc. cit.*) records m. p. 82—83°. The dimethyl ester (9·8 g.) was boiled under reflux for ½ hour with methanol (30 c.c.) containing potassium hydroxide (1·9 g.). Methanol (15 c.c.) was then distilled off, water (30 c.c.) added, and the solution extracted with ether. Distillation of the ether gave unchanged dimethyl ester (5·0 g.). Acidification of the aqueous solution precipitated the methyl ester (4·3 g.), m. p. 175—181°. Two recrystallisations from benzene–light petroleum (b. p. 80—100°) gave the pure ester, m. p. 179·5—181°. Salmon-Legagneur (*loc. cit.*) records m. p. 183—184°.

αα-*Diphenylglutarodinitrile*.—To a stirred solution of diphenylacetonitrile (19·3 g.) in *tert.*-butyl alcohol (50 c.c.) containing 1 c.c. of 30% methanolic potassium hydroxide was added acrylonitrile (redistilled, 8·0 g.). The temperature was maintained at 50° first by warming, then by controlled addition of the acrylonitrile. After complete addition (20 minutes) the temperature was kept at 50° for a further 3 hours. Water (100 c.c.) was then added, and the cooled mixture extracted with ether. The dried extract (Na_2SO_4) was freed from solvent by distillation under reduced pressure. The residual pale yellow oil solidified and recrystallisation from ethanol yielded αα-*diphenylglutarodinitrile* (20·1 g.) in colourless prisms, m. p. 71·5—72·5° (Found: C, 83·2; H, 5·9. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%).

The α- *and the* γ-*Methyl Ester of* αα-*Diphenylglutaric Acid*.—αα-Diphenylglutarodinitrile (10·4 g.) was boiled under reflux for 36 hours with acetic acid (20 c.c.) and concentrated hydro-

bromic acid (40 c.c.). The cooled solution was poured on ice (200 g.), and the fawn-coloured solid filtered off (11·7 g.) and dried *in vacuo* (m. p. 158—172°). The solid was boiled under reflux for 4 hours with potassium hydroxide (50 g.) in water (50 c.c.), and the cooled solution poured into water (150 c.c.) and acidified. The white precipitate was filtered off and recrystallised from aqueous acetic acid. The acid (10·4 g.) separated in colourless needles, m. p. 195—197°. Salmon-Legagneur (*Compt. rend.*, 1941, **213**, 183) records m. p. 183° and Trivedi, Phalnikar, and Nargund (*J. Univ. Bombay*, 1942, **10**, Part 5, 136) quote m. p. 193—194° for αα-diphenylglutaric acid. The acid (10·4 g.) was esterified as for the corresponding succinic acid (see above). The γ-methyl ester separated from benzene–light petroleum (b. p. 80—100°) in colourless prisms (7·3 g.). The m. p. on drying at 100° was 110—112°, but prolonged drying at 100° *in vacuo* raised it to 124—125°, and subsequent recrystallisation and drying to 125—125·5°. Salmon-Legagneur (*Compt. rend.*, 1941, **213**, 183) records m. p. 108°. Distillation of the ether from the neutral fraction yielded the dimethyl ester (3·3 g.), m. p. 53—55°. Salmon-Legagneur records 64—65°. The dimethyl ester (3·3 g.) was boiled under reflux for ½ hour with potassium hydroxide (0·65 g.) in methanol (30 c.c.). The mixture, worked up as above, yielded unchanged dimethyl ester (1·2 g.), and the α-methyl ester (1·6 g.) in colourless prisms, m. p. 127—129·5°, unchanged by prolonged drying *in vacuo*. Salmon-Legagneur records m. p. 129° for this ester.

Reactions of Half Esters.

Peroxide of 2-Methyl Hydrogen 3-Nitrophthalate with Benzene.—2-Methyl hydrogen 3-nitrophthalate (22·5 g.) was boiled under reflux for 1 hour with purified thionyl chloride (25 c.c.; b. p. 75—76°) which had been fractionated over quinoline and refractionated over linseed oil. Removal of the excess of thionyl chloride under reduced pressure gave the acid chloride in white needles. To a stirred solution of the acid chloride in chloroform (40 c.c.) was added a solution of sodium hydroxide (4·5 g.) in water (10 c.c.), followed by hydrogen peroxide (20-vol.; 60 c.c.). The temperature was kept at 0—5° for 1½ hours. The bulky white precipitate was filtered off and dried *in vacuo*. A further 0·8 g. was obtained by addition of methanol (200 c.c.) to the chloroform layer. The total yield of the *peroxide* was 19·9 g. (purity by titration, 98·3%). The peroxide (18·5 g.) was boiled under reflux for 18 hours with benzene (100 c.c.). The cooled solution on extraction with 5% aqueous sodium carbonate and acidification of the extracts gave crude 2-methyl hydrogen 3-nitrophthalate (8·9 g.), m. p. 148—152°. Distillation of the benzene gave an orange solid, which distilled at 135—145°/3 × 10^{-2} mm., to give *methyl 3-nitrodiphenyl-2-carboxylate* as a colourless oil (9·3 g.), which solidified. Crystallisation from aqueous alcohol gave colourless prisms, m. p. 121·5—122·5° (Found: C, 65·5; H, 4·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%). The methyl ester (8·7 g.) on hydrolysis with 5% potassium hydroxide in aqueous alcohol yielded *3-nitrodiphenyl-2-carboxylic acid* (7·4 g.) in colourless prisms, m. p. 200·5—201·5° from aqueous alcohol (Found: C, 64·4; H, 3·9. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7%). The crude 3-nitrodiphenyl-2-carboxylic acid (6·6 g.) was powdered and stirred with concentrated sulphuric acid (20 c.c.) (5 minutes), the temperature raised to 60° for 5 minutes, and the mixture poured on ice (100 g.). The yellow precipitate was filtered off, washed well with 5% sodium carbonate solution, then with water, and dried at 100°. The *1-nitrofluorenone* (5·9 g.) melted at 187—188°, raised on sublimation under reduced pressure and recrystallisation from benzene to 188·5—189·5° (lemon-yellow prisms) (Found: C, 69·1; H, 3·2. $C_{13}H_7O_3N$ requires C, 69·3; H, 3·1%). Finely powdered 1-nitrofluorenone (2·0 g.) was boiled under reflux with alcohol (120 c.c.) and ammonia (*d* 0·88; 15 c.c.). Hydrogen sulphide was passed in for 3 hours, during which the fluorenone dissolved. The solution, concentrated to 25 c.c., was diluted with water (125 c.c.) and filtered. The orange residue was 6 times extracted with boiling 3N-hydrochloric acid (25 c.c. portions). Basification of the filtered extract with ammonia precipitated 1-aminofluorenone (1·43 g.) as an orange solid, m. p. 114—117°, raised on recrystallisation from aqueous alcohol and subsequently from light petroleum (b. p. 80—100°) to 118·5—119·5° (orange plates and needles, the latter transforming sharply into the former near the m. p.). The acetyl derivative formed yellow needles, m. p. 138—139°, from aqueous alcohol or light petroleum (b. p. 80—100°) (Huntress, Pfister, and Pfister, *J. Amer. Chem. Soc.*, 1942, **64**, 2847, record m. p. 118—118·5° for 1-aminofluorenone and 138—138·3° for the acetyl derivative).

The use of phosphorus pentachloride in the preparation of the acid chloride from 2-methyl hydrogen 3-nitrophthalate led to rather lower yields of peroxide, but the latter when decomposed in benzene and submitted to the above series of reactions yielded only 1-nitrofluorenone,

m. p. 188·5—189·5°, identical with that obtained above. No trace of the isomeric 4-nitro-compound could be detected.

Friedel–Crafts Reaction (Benzene) with 1-Methyl Hydrogen 3-Nitrophthalate.—1-Methyl hydrogen 3-nitrophthalate (15 g.) was boiled under reflux for 1½ hours with purified thionyl chloride (25 c.c.), and the excess of chloride removed under reduced pressure. The acid chloride in dry thiophen-free benzene (75 c.c.) was added dropwise to a stirred suspension of freshly ground aluminium chloride (20 g.) in dry thiophen-free benzene (75 c.c.). The temperature was kept at 0—5° during the addition (1 hour); the colour of the mixture changed through green to dark blue and finally almost to black. The mixture was stirred for a further hour, kept at room temperature overnight, and decomposed with ice (200 g.) and concentrated hydrochloric acid (50 c.c.). A considerable quantity of insoluble material was filtered off. The benzene layer, washed well with dilute acid and with 5% aqueous sodium carbonate, on removal of solvent and distillation of the residue, gave a viscous yellow oil (4·8 g.). This oil was boiled under reflux for ½ hour with methanol (20 c.c.) (in order to remove anhydride), diluted with ether (100 c.c.), and extracted with 5% aqueous sodium carbonate. Distillation of the ether yielded a viscous yellow oil (3·0 g.) which was boiled under reflux for 18 hours with 10% aqueous potassium hydroxide (40 c.c.). The solution was cooled, diluted with water, extracted with ether, acidified, and re-extracted with ether. Distillation of the ether from the second dried extract yielded a brown solid (2·5 g.). One recrystallisation from 80% acetic acid yielded 6-nitrobenzophenone-2-carboxylic acid (0·5 g.), m. p. 223—233°, raised on recrystallisation from aqueous acetic acid to 236—237° (colourless needles) (Hayashi *et al.*, *Bull. Chem. Soc. Japan*, 1936, **11**, 191, quote m. p. 236—237°). The mother-liquors on concentration yielded first a further quantity of the same acid and then 3-nitrobenzophenone-2-carboxylic acid in colourless needles (0·3 g.), m. p. 160—162°, raised on subsequent recrystallisation to 161·5—162·5°. Hayashi *et al.* quote m. p. 160—161°. The latter acid (0·19 g.) was stirred with copper chromite (0·5 g.) in quinoline (5 c.c.) at 165—175°. The product, worked up as for 1-benzyl hydrogen 4-nitrophthalate, on recrystallisation from alcohol gave 3-nitrobenzophenone (0·087 g.) in colourless needles, m. p. 93·5—94·5°. Geigy and Koenigs (*Ber.*, 1885, **18**, 2401) quote m. p. 94—95°.

Friedel–Crafts Reaction (Benzene) with 2-Methyl Hydrogen 3-Nitrophthalate.—2-Methyl hydrogen 3-nitrophthalate (15 g.) was converted into the acid chloride and treated with aluminium chloride in benzene as for the 1-methyl ester. The product distilled at 170—180°/2 × 10^{-2} mm. as a pale yellow oil (15·3 g.). After removal of anhydride as above, the residue (14·3 g.) solidified on trituration with methanol to a white solid, m. p. 85—95°. Two recrystallisations from methanol gave pure *methyl 3-nitrobenzophenone-2-carboxylate* (12·0 g.) in colourless prisms, m. p. 93·5—94·5° (Found: C, 63·4; H, 3·7. $C_{15}H_{11}O_5N$ requires C, 63·2; H, 3·9%). Hydrolysis of the ester with concentrated hydrochloric acid containing a little dioxan yielded 3-nitrobenzophenone-2-carboxylic acid in long colourless prisms, m. p. 162·5—163·5°, undepressed on admixture with the acid, m. p. 161·5—162·5°, obtained from the 1-methyl ester. The mother-liquors from the recrystallisation of methyl 3-nitrobenzophenone-2-carboxylate yielded on evaporation a viscous light brown oil, which was boiled under reflux for 8 hours with concentrated hydrochloric acid (20 c.c.), water (10 c.c.), and dioxan (1 c.c.). The acidic product (0·8 g.) on recrystallisation from aqueous acetic acid gave 6-nitrobenzophenone-2-carboxylic acid (0·2 g.) in colourless needles, m. p. 236—238°, identical with the corresponding compound obtained from the isomeric acid ester.

Friedel–Crafts Reaction (Toluene) with 1-Methyl Hydrogen 3-Nitrophthalate.—The acid ester (15 g.) was converted into the acid chloride, and the Friedel–Crafts reaction carried out as previously but with dry toluene in place of benzene. The reaction mixture, worked up as before, gave on distillation a pale yellow oil (6·7 g.; b. p. 175—195°/1·5 × 10^{-2} mm.). After removal of any 3-nitrophthalic anhydride by treatment with methanol, the residue (6·0 g.) largely solidified. Recrystallisation from ethanol yielded pure *methyl 4′-methyl-6-nitrobenzophenone-2-carboxylate* (3·5 g.) in colourless prisms, m. p. 162—163° (Found: C, 64·4; H, 4·6. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·3%). The mother-liquors on fractional crystallisation from ethanol gave an unidentified *isomer* (0·15 g.) in colourless prisms, m. p. 107·5—108·5° (Found: C, 64·4; H, 4·5%), which depressed the m. p. of both methyl 4′-methyl-6- and -3-nitrobenzophenone-2-carboxylate. Methyl 4′-methyl-6-nitrobenzophenone-2-carboxylate (2·0 g.; m. p. 162—163°) was boiled under reflux for 1 hour with a mixture of concentrated sulphuric acid (6 c.c.), water (3 c.c.), and acetic acid (10 c.c.). The cooled solution was diluted and extracted with ether, and the ethereal extract washed with 5% aqueous sodium carbonate. Acidification of the alkaline extract gave 4′-methyl-6-nitrobenzophenone-2-carboxylic acid

(1·85 g.) as a fawn-coloured crystalline powder, m. p. 217·5—218·5°, raised on recrystallisation from aqueous acetic acid to 219·5—220·5° (colourless prisms) (see also Table 2, p. 560). The above acid (1·0 g.) on decarboxylation with copper chromite and quinoline at 165—185° (3 hours) yielded 4′-methyl-2-nitrobenzophenone (0·74 g.), m. p. 151—153°, raised on recrystallisation from aqueous alcohol to 154—155° (large flattened needles). Boëtius and Römisch (*Ber.*, 1935, **68**, 1931) quote m. p. 155°.

The isomeric ester (m. p. 107·5—108·5°; 0·09 g.) obtained above yielded on acid hydrolysis an unidentified *acid* (0·07 g.), m. p. 206·5—210°, raised on recrystallisation from aqueous acetic acid to 211—212° (colourless needles) (Found: C, 63·5; H, 3·8. $C_{15}H_{11}O_5N$ requires C, 63·2; H, 3·9%). The acid depressed the m. p. of both 4′-methyl-6-nitrobenzophenone-2-carboxylic acid (m. p. 220·5°) and of 4′-methyl-3-nitrobenzophenone-2-carboxylic acid (m. p. 189°) and must be, therefore, 2′(or 3′)-methyl-3(or 6)-nitrobenzophenone-2-carboxylic acid.

Friedel–Crafts Reaction (*Toluene*) *with 2-Methyl Hydrogen 3-Nitrophthalate.*—The 2-methyl ester (9·0 g.) was employed as for the 1-methyl ester (above). The product distilled at 160—180°/9 × 10^{-3} mm., to give a pale yellow oil (11·0 g.), which solidified on trituration with methanol. Six recrystallisations from methanol gave pure *methyl 4′-methyl-3-nitrobenzophenone-2-carboxylate* (5·1 g.) in colourless prisms, m. p. 114—115° (Found: C, 64·2; H, 4·4. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·3%). No pure isomeric ester could be isolated by fractional crystallisation of the mother-liquors, or by fractional crystallisation of the corresponding acids. Methyl 4′-methyl-3-nitrobenzophenone-2-carboxylate (4·0 g.) was boiled under reflux for 4 hours with acetic acid (12 c.c.), sulphuric acid (8 c.c.), and water (4 c.c.). The product, worked up as previously, gave unchanged ester (0·5 g.) and an *acid* (2·9 g.), which crystallised from aqueous acetic acid in long colourless prisms, m. p. 186—188°, raised on recrystallisation to 188—189° (Found: C, 63·3; H, 3·8. $C_{15}H_{11}O_5N$ requires C, 63·2; H, 3·9%) (see also Table 2, p. 560). The above acid (1·0 g.) on decarboxylation with copper chromite and quinoline (2 hours at 175°) gave 4′-methyl-3-ntrobenzophenone 0·67 g.), m. p. 112·5—114°, undepressed on admixture with an authentic specimen, m. p. 112·5—114°, prepared by Limpricht and Lenz's method (*Annalen*, 1895, **286**, 307).

1-*Methyl* 2-*Phenyl* 3-*Nitrophthalate.*—The acid chloride, prepared as described above from 1-methyl hydrogen 3-nitrophthalate (7·5 g.), in chloroform (25 c.c.), was cooled to 0°, and an ice-cold solution of phenol (4·5 g.) in 5% aqueous sodium hydroxide (50 c.c.) added with vigorous stirring. The mixture was stirred for a further hour, then set aside overnight, and the organic layer then washed with water, dried, and distilled free from solvent. *1-Methyl 2-phenyl 3-nitrophthalate* separated from methanol in colourless prisms (6·3 g.), m. p. 123·5—124·5° (Found: C, 59·9; H, 3·5. $C_{15}H_{11}O_6N$ requires C, 59·8; H, 3·7%). The filtrates on storage for 48 hours deposited a few crystals, m. p. 160—162°, which proved to be 1-methyl hydrogen 3-nitrophthalate. The residue was taken up in ether and washed with 5% sodium carbonate solution, and the ether distilled off from the dried (Na_2SO_4) extract. The residue (1·0 g.) did not solidify on storage or on trituration.

2-*Methyl* 1-*Phenyl* 3-*Nitrophthalate.*—The 2-methyl ester (4·5 g.) was employed as described above for the 1-methyl ester. The product, on crystallisation from aqueous methanol, gave *2-methyl 1-phenyl 3-nitrophthalate* (3·2 g.) in colourless prisms, m. p. 108·5—109·5° (Found: C, 60·1; H, 3·6. $C_{15}H_{11}O_6N$ requires C, 59·8; H, 3·7%). The filtrates on dilution precipitated an oil, which did not solidify on long storage at 0°. The m. p. of the crystalline product was strongly depressed on admixture with that prepared from the 1-methyl ester.

Kinetic Studies of 1-*Methyl and* 2-*Methyl Hydrogen* 3-*Nitrophthalate.*—The two monomethyl esters (5·00 g.) were separately heated under reflux with unpurified thionyl chloride (20 c.c.) for a known time. After removal of excess of thionyl chloride as rapidly as possible on the water-bath under reduced pressure, the residue was treated with 10% aqueous sodium hydrogen carbonate (100 c.c.) and boiled gently under reflux for 15 minutes, more bicarbonate being added, if necessary, to maintain an excess. The resulting mixture, cooled to 0°, was made acid with concentrated hydrochloric acid and thoroughly extracted with ether. Distillation of the ether from the dried extract gave the mixture of half-esters, which was dried at 100° under reduced pressure before esterification. The esterification was carried out by boiling under reflux for 24 hours with absolute methanol (25 c.c.) containing concentrated sulphuric acid (2·5 c.c.). The cooled solution was diluted with water (50 c.c.) and extracted with ether, and the ethereal extract was washed with 5% aqueous sodium carbonate (4 × 30 c.c.). Removal of the ether in a tared flask gave the neutral fraction (diester), whereas acidification of the carbonate washings, extraction with ether, and removal of the solvent gave the acid fraction (monoester). Both fractions were dried at 100° under reduced pressure before being weighed.

The proportions of the 1-methyl and 2-methyl esters present in the product obtained on hydrolysis of the acid chloride were calculated from a knowledge of the proportions of acid and neutral esters obtained by the application of the procedure outlined above to each of the pure half-esters. Thus, the 1-methyl ester (5·00 g.) gave 4·533 g. of acid ester and 0·374 g. of neutral ester. The latter is equivalent to $225/239 \times 0{\cdot}374$ g. $= 0{\cdot}352$ g. of acid ester, and thus the total acid ester recovered is 4·885 g. The percentage of acid ester in the total recovered material, *i.e.*, the percentage unesterified, is $4{\cdot}533/4{\cdot}885 \times 100 = 92{\cdot}8\%$. In similar manner, when the pure 2-methyl ester was used, the percentage unesterified was 6·3%. If it is assumed that the rate of esterification in each case is unaffected by the presence of the isomeric half-ester, the percentage of 1-methyl ester in any mixture of the two isomeric half-esters is given by $P = 100(U - 6{\cdot}3)/(92{\cdot}8—6{\cdot}3)$, where U is the percentage of half-ester unesterified after 24 hours. The results obtained in this way are shown in the figure.

Peroxide of 1-*Methyl Hydrogen* 4-*Nitrophthalate* (cf. Hey and Walker, *J.*, 1948, 2217).—1-Methyl hydrogen 4-nitrophthalate (22·5 g.) was boiled under reflux for 1 hour with purified thionyl chloride (20 c.c.), and the excess of chloride removed under reduced pressure. The semi-solid acid chloride was converted into the peroxide, and the latter decomposed in boiling benzene (200 c.c.). The neutral product on distillation gave a pale yellow oil (8·2 g.; b. p. 130—145°/$1{\cdot}5 \times 10^{-2}$ mm.), which did not completely solidify on storage. The product was hydrolysed with 10% aqueous sodium hydroxide, and the crude acid (7·9 g.) stirred with concentrated sulphuric acid (20 c.c.) at 30—40° until dissolution was complete. The reaction mixture was poured on ice, basified with sodium hydroxide, and filtered. The crude mixture of nitrofluorenones (5·0 g.) was sublimed under reduced pressure (approx. 200°), to yield lemon-yellow prisms (3·1 g.), m. p. 182—190°. Fourteen recrystallisations from benzene gave 3-nitrofluorenone (0·1 g.) in yellow needles, m. p. 231—232°. Ray and Barrick (*J. Amer. Chem. Soc.*, 1948, **70**, 1492) quote m. p. 236°. Laborious fractional crystallisation of the mother-liquors yielded 2-nitrofluorenone (0·05 g.) in yellow needles, m. p. 218—219°, undepressed on admixture with an authentic specimen, m. p. 219° (Heilbron, Hey, and Wilkinson, *J.*, 1938, 115). The m. p. was strongly depressed on admixture with the 3-nitrofluorenone obtained above. The use of phosphorus pentachloride in place of thionyl chloride in the preparation of the acid chloride led to a similar yield of peroxide (65%, purity 98%). Decomposition in benzene and fractional crystallisation of the nitrofluorenone mixture led to the isolation of both 2-nitrofluorenone (m. p. 219—220°) and 3-nitrofluorenone (m. p. 230—231·5°).

Friedel–Crafts Reaction (*Benzene*) *with* 1-*Methyl Hydrogen* 4-*Nitrophthalate*.—The acid ester (15 g.) in dry benzene (50 c.c.) was treated with phosphorus pentachloride (16·7 g.). After 1 hour at room temperature, the mixture was boiled under reflux for 15 minutes and the volatile products were removed under reduced pressure. The reaction with benzene was carried out as described for the 3-nitrophthalic acid esters. The product distilled at 150—170°/5×10^{-2} mm. to yield a pale yellow oil (8·9 g.), which solidified on trituration with methanol. Recrystallisation from methanol gave methyl 4-nitrobenzophenone-2-carboxylate in colourless prisms, m. p. 124—125°. Rainer (*Monatsh.*, 1908, **29**, 434) records m. p. 123·5—124°. Concentration of the mother-liquors yielded an oil from which no pure ester could be isolated. Acid hydrolysis of the crystalline ester gave 4-nitrobenzophenone-2-carboxylic acid in white plates, m. p. 214—215°. Rainer (*loc. cit.*) quotes m. p. 212° for this acid prepared by a Friedel–Crafts reaction upon the anhydride. The mother-liquors from the crystallisation of the ester were hydrolysed with boiling 4N-hydrochloric acid (100 c.c.; 12 hours). The acidic product (5·8 g.) on recrystallisation from aqueous ethanol (6 times) and from benzene–light petroleum (b. p. 60—80°) (3 times) gave 5-nitrobenzophenone-2-carboxylic acid in long colourless needles, m. p. 163—164°. Rainer (*Monatsh.*, 1908, **29**, 179) quotes m. p. 164—165° (corr.).

In an attempt to avoid rearrangement, the reaction was carried out as follows: The acid ester (7·5 g.) in dry ether (30 c.c.) was treated with purified thionyl chloride (10 c.c.). The temperature was slowly raised to 25° and kept thereat for 2 hours. Removal of the ether and excess of thionyl chloride at 25° under reduced pressure yielded the acid chloride as a viscous, fawn-coloured semi-solid. The condensation with benzene was carried out as before, but care was taken to ensure that the reaction temperature did not rise above 10° during 3 hours. Distillation of the product (5·15 g.), b. p. 150—160°/$1{\cdot}3 \times 10^{-2}$ mm., followed by recrystallisation from methanol, gave methyl 4-nitrobenzophenone-2-carboxylate (2·0 g.), m. p. 124—125°.

Friedel–Crafts Reaction (*Toluene*) *with* 1-*Methyl Hydrogen* 4-*Nitrophthalate*.—The 1-methyl ester (22·5 g.) was converted into the acid chloride with purified thionyl chloride and submitted to the Friedel–Crafts reaction with toluene, as described above for the 3-nitrophthalates. The product (23·0 g.), b. p. 180—190°/0·35 mm., solidified. Recrystallisation from methanol

(8 times) gave *methyl 4′-methyl-4-nitrobenzophenone-2-carboxylate* (5·0 g.) in colourless prisms, m. p. 132—133° (Found: C, 64·5; H, 4·4. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·3%). No pure isomeric ester could be obtained by fractional crystallisation of the mother-liquors, but a residue (A), m. p. 83—87°, was hydrolysed (see below). Acid hydrolysis yielded 4′-methyl-4-nitrobenzophenone-2-carboxylic acid, m. p. 191—192·5°, raised on recrystallisation from aqueous acetic acid to 192—193° (colourless prisms) (see also Table 3, p. 562). Decarboxylation with copper chromite (2 hours at 190°), carried out as described above, gave 4′-methyl-4-nitrobenzophenone, m. p. 122—123°, in colourless needles from benzene–light petroleum (b. p. 80—100°). Limpricht and Samietz (*Annalen*, 1895, **286**, 321) record m. p. 122—124°. Acid hydrolysis of the ester residue (A) obtained above (1·5 g., colourless needles, m. p. 83—87°) gave crude 4′-methyl-5-nitrobenzophenone-2-carboxylic acid (1·35 g.), m. p. 189—212°. Recrystallisation from aqueous acetic acid yielded the pure acid in colourless prisms, m. p. 217·5—218·5° (see, further, Table 3). Decarboxylation of 4′-methyl-5-nitrobenzophenone-2-carboxylic acid yielded 4′-methyl-3-nitrobenzophenone (59%). The ketone separated from aqueous alcohol in a mixture of needles and prisms. The former changed into the latter at 110·5° and the homogeneous material melted at 113—114°, undepressed on admixture with an authentic specimen (Limpricht and Lenz, *Annalen*, 1895, **286**, 307).

Anilide of 1-*Methyl Hydrogen* 4-*Nitro*isophthalate.—1-Methyl hydrogen 4-nitro*iso*phthalate (2·25 g.) was boiled under reflux for 2 hours with purified thionyl chloride. On removal of the excess of chloride under reduced pressure the acid chloride formed white needles. To the acid chloride in pyridine (6 c.c.) was added dropwise with shaking a solution of aniline (1·4 g.) in pyridine (5 c.c.). The crude anilide, isolated in the usual manner, was obtained as a fawn-coloured crystalline solid (2·6 g.), m. p. 165—168°. Recrystallisation from aqueous alcohol or benzene–light petroleum (b. p. 80—100°) gave the pure *anilide* in very pale yellow needles, m. p. 170·5—171·5° (Found: C, 60·2; H, 4·1. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%). No trace of an isomeric ester anilide could be detected.

Peroxide of 1-*Methyl Hydrogen* 4-*Nitro*iso*phthalate.*—The acid ester (7·5 g.) was boiled under reflux for 2 hours with crude thionyl chloride and converted into the peroxide (6·5 g.) as described above for 2-methyl hydrogen 3-nitrophthalate. The peroxide (6·2 g.) was boiled under reflux for 21 hours with dry thiophen-free benzene (50 c.c.). The resultant red solution deposited, on cooling, crystals of the acid ester. After extraction with aqueous sodium carbonate, the benzene solution was dried ($CaCl_2$). Removal of the benzene and distillation of the residue yielded methyl 6-nitrodiphenyl-3-carboxylate (2·6 g.) as a pale yellow viscous oil, which did not solidify. Hydrolysis of the ester by refluxing it for 1½ hours with a mixture of acetic acid (10 c.c.), concentrated sulphuric acid (4 c.c.), and water (2 c.c.) gave 6-nitrodiphenyl-3-carboxylic acid (2·2 g.), which separated from aqueous acetic acid and from ethanol in bright yellow needles, m. p. 224·5—226°. France, Heilbron, and Hey (*J.*, 1939, 1292) recorded m. p. 220—221° (yellow plates) for this acid. The acid (1·5 g.) was decarboxylated with copper chromite in quinoline (3 hours at 200°) in the usual way. The acidic fraction gave unchanged acid (0·6 g.). The neutral fraction was extracted with hot light petroleum (b. p. 40—60°), and the extract concentrated. 2-Nitrodiphenyl was deposited in colourless prisms, m. p. 30°, raised on recrystallisation from the same solvent to m. p. 35—36°, undepressed on admixture with an authentic specimen, m. p. 36·5°.

Peroxide of 4-*Methyl Hydrogen* 2-*Nitroterephthalate.*—The acid ester (10·0 g.) was boiled under reflux for 2 hours with crude thionyl chloride (20 c.c.), the excess of the latter removed under reduced pressure, and the residual acid chloride in alcohol-free chloroform (30 c.c.) converted into the peroxide (9·5 g.) as for the *iso*phthalate. The peroxide (9·5 g.) in the form of a white powder was boiled under reflux for 18 hours with dry thiophen-free benzene (100 c.c.). The neutral fraction, worked up as for the *iso*phthalate, distilled at 155—165°/0·5 mm. to give a pale yellow viscous oil (4·3 g.), which did not solidify. The crude methyl 2-nitrodiphenyl-4-carboxylate was hydrolysed with sulphuric acid in aqueous acetic acid, to give the acid (3·7 g.), which separated from aqueous acetic acid and subsequently from benzene in yellow needles or plates, m. p. 190·5—192·5°, undepressed on admixture with an authentic specimen, m. p. 191°, prepared by Grieve and Hey (*J.*, 1932, 1894). The mother-liquors were evaporated to dryness and extracted with hot benzene. The extract yielded a small amount of 2-nitrodiphenyl-4-carboxylic acid. The residue, m. p. 259—263°, crystallised from water and subsequently from chloroform–ether–light petroleum (b. p. 80—100°) in colourless prisms, m. p. 270—271·5°, undepressed on admixture with authentic 2-nitroterephthalic acid.

Anilide from β-*Methyl Hydrogen* αα-*Diphenylsuccinate.*—The β-methyl ester (2·84 g.) was boiled under reflux for ½ hour with purified thionyl chloride. The acid chloride in dry

benzene (20 c.c.) was treated with aniline (1·9 g.) in dry benzene, and the mixture shaken, kept overnight, and worked up in the usual way. The neutral fraction (3·1 g.) solidified when kept. Five successive recrystallisations from benzene–light petroleum and then from ethanol gave αα*N*-triphenylsuccinimide, m. p. 169·5—170·5° (Found: C, 80·3; H, 5·0. Calc. for $C_{22}H_{17}O_2N$: C, 80·7; H, 5·2%). Salmon-Legagneur and Soudan (*Compt. rend.*, 1944, **218**, 682) quote m. p. 163°.

Methylanilide from β-*Methyl Hydrogen* αα-*Diphenylsuccinate.*—To the acid chloride from the β-methyl ester (5·0 g.) in dry benzene (20 c.c.) were added methylaniline (2·5 g.) in dry benzene (10 c.c.) and pyridine (2 drops). The mixture was heated under reflux on the steam-bath for 1 hour and worked up in the usual manner. The neutral fraction (6·3 g.) was a fawn-coloured gum, which did not completely solidify on storage. The product was chromatographed on alumina. Elution with benzene yielded buff-coloured prisms (A) (2·12 g.), m. p. 140—147°, followed by a small amount of colourless gum (0·25 g.); elution with ether and with methanol yielded white prisms (B) (1·44 g.), m. p. 136—139°. The compound (A), on recrystallisation from benzene–light petroleum (b. p. 80—100°), gave the *methylanilide* of methyl αα-diphenylsuccinate in colourless prisms, m. p. 149·5—150·5° (Found: C, 77·1; H, 6·1. $C_{24}H_{23}O_3N$ requires C, 77·2; H, 6·2%). The fraction (B) separated from light petroleum (b. p. 80—100°) in thick prisms, m. p. 136—138° [mixed m. p. with (A) 117—128°], but further recrystallisation from benzene–light petroleum (b. p. 80—100°) gave αα-*diphenylsuccinobismethylanilide* in colourless plates, m. p. 155—156° (Found: C, 80·6; H, 6·2; N, 6·3. $C_{30}H_{28}O_2N_2$ requires C, 80·4; H, 6·3; N, 6·25%).

Synthesis of the α-*Methyl Ester* β-*Methylanilide of* αα-*Diphenylsuccinic Acid* (*Methyl* αα-*Diphenylsuccinomethylanilide*).—The silver salt (2·05 g.) of the α-methyl ester in dry ether (10 c.c.) at 0—10° was treated with purified thionyl chloride (1·0 g.) in dry ether (5 c.c.) containing pyridine (1 drop). After this had stood, with occasional shaking, at 0—10° for 5 minutes, methylaniline (0·6 g.) was added, and the mixture shaken at the same temperature for 10 minutes. Ether (25 c.c.) was then added, the mixture filtered, and the residue washed with dry ether (20 c.c.). The combined ethereal extracts, thoroughly washed with 5N-hydrochloric acid and with 5% aqueous sodium carbonate, were dried (Na_2SO_4), and the solvent was distilled off. The residue (1·8 g.) slowly solidified on trituration with light petroleum. Two recrystallisations from ethyl acetate–light petroleum (b. p. 80—100°) gave colourless prisms (0·19 g.), m. p. 154—166°, raised on recrystallisation from benzene–light petroleum to 166—167° (Found: C, 68·3; H, 4·8%). Concentration of the mother-liquors gave clusters of prisms (1·3 g.), m. p. 143—148°, raised on recrystallisation from benzene–light petroleum (b. p. 80—100°) to 149—150°. The m. p. was undepressed on admixture with the ester methylanilide (A) (above).

When the silver salt of the β-methyl ester (2·9 g.) was treated with thionyl chloride and with methylaniline as described above for the α-methyl ester, the neutral fraction on recrystallisation from benzene–light petroleum (b. p. 80—100°) gave only the *anhydride* of the β-methyl ester in prisms, m. p. 115—118° (Found: C, 74·0; H, 5·6. $C_{34}H_{30}O_7$ requires C, 74·2; H, 5·5%).

Diethylamide from γ-*Methyl Hydrogen* αα-*Diphenylglutarate.*—The γ-methyl ester (3·6 g.) was boiled under reflux for 1 hour with purified thionyl chloride (15 c.c.), and the excess of the latter removed under reduced pressure. The oily acid chloride in dry benzene (15 c.c.) was treated with diethylamine (2·0 g.) in dry benzene (15 c.c.). The mixture was boiled under reflux for 20 minutes, cooled, and thoroughly washed with acid and with 5% aqueous sodium carbonate. The residue (3·4 g.) after distillation of the benzene was chromatographed on an alumina column. Elution with benzene–light petroleum (b. p. 80—100°) yielded a pale yellow gum (1·80 g.). Subsequent elution with benzene and later with ether yielded a diethylamide of methyl hydrogen αα-diphenylglutarate (Diethylamide A) (1·53 g.) in colourless prisms, m. p. 99·5—100° from light petroleum (b. p. 80—100°) (Found: C, 75·0; H, 7·7. $C_{23}H_{27}O_3N$ requires C, 74·8; H, 7·6%), shown below to be *methyl* NN-*diethyl*-αα-*diphenylglutaramate*. The gummy fraction from the chromatogram was rechromatographed and the first of these new fractions (0·25 g.), m. p. 88—107°, was depressed on admixture with diethylamide A. The later fractions consisted entirely of more of the diethylamide A. The first fraction was thrice recrystallised from benzene–light petroleum and separated by hand into colourless prisms (27 mg.), m. p. 112—117°, and opaque prisms, m. p. 98—103°. The former, after recrystallisation from benzene–light petroleum, gave the isomeric diethylamide (Diethylamide B), m. p. 115·5—117·5° (Found: C, 74·5; H, 7·6. $C_{23}H_{27}O_3N$ requires C, 74·8; H, 7·6%), which, by exclusion, is *methyl* NN-*diethyl*-γγ-*diphenylglutaramate*.

Synthesis of γ-Diethylamide of α-Methyl Hydrogen αα-Diphenylglutarate (*Methyl* NN-*Diethyl-αα-diphenylglutaramate*).—To the silver salt of the α-methyl ester in dry ether was added purified thionyl chloride (1·2 g.) in dry ether (5 c.c.), the temperature being kept at 0—5°. After this had been kept, with occasional shaking, at 0—5° for 10 minutes, diethylamine (1·0 g.) in dry ether (5 c.c.) was added with cooling. The mixture was kept for 10 minutes at room temperature and worked up in the usual way. The neutral fraction (0·6 g.) was chromatographed on alumina. Elution with ether gave the diethylamide A (0·25 g.), m. p. 97—99°, raised on recrystallisation to 99—100° and undepressed on admixture with the diethylamide A obtained as above. No other product could be isolated.

When the silver salt technique, as outlined above, was applied to the γ-methyl ester only inconclusive results were obtained.

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101. *The Catalytic Deuteration of Organic Compounds. Part I. Deuteration and Disproportionation.*

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Bloch and Rittenberg's method of preparing deuteriocholesterol by a platinum-catalysed exchange reaction between the sterol and deuterium oxide has been applied to a series of simpler compounds. Each contained representative features of sterol molecules, and the deuteration results have allowed these compounds to be placed in order of increasing facility of exchange. Considerable amounts of deuterium were found in the products when the original compounds underwent a disproportionation reaction in deuterium oxide.

THE preparation of deuteriocholesterol containing up to 5% of deuterium by the treatment of cholesterol with deuterium oxide and acetic acid at 120° in presence of a platinum catalyst has been described by Bloch and Rittenberg (*J. Biol. Chem.*, 1943, **149**, 505). According to these workers the deuterium was introduced into the side chain and the ring system of the sterol, while a destruction of cholesterol took place parallel with the extent of deuteration.

In the present investigation the applicability of this reaction to the deuteration of some simpler compounds has been studied, and the resulting information has been used (see following paper) in a re-examination of Bloch and Rittenberg's work on cholesterol and in a deuteration of ergosterol by similar methods.

The simpler compounds were chosen from saturated and unsaturated aliphatic and alicyclic hydrocarbons: benzene and *cyclo*hexanol were also examined for further comparisons.

Some indication of the influence of structure on the extent of the exchange reaction may be seen in Table 1 which shows the amounts of deuterium introduced under comparable reaction conditions into the reaction products, results being included for two series of experiments in which the catalyst preparations were of different activity.

It is seen that, whereas relatively little exchange of the hydrogen atoms in the saturated *n*-hexane and *cyclo*hexane molecules took place, the introduction of a double bond resulted in considerably greater exchange, a similar effect being also produced to a lesser extent by the presence of a hydroxyl group. An exchange reaction between ethylene and deuterium oxide in presence of a nickel catalyst has been discussed by Horiuti and Polanyi (*Trans. Faraday Soc.*, 1934, **30**, 1164); the mechanism suggested involved chemisorption at the double bond accompanied by bond-opening, transfer of a hydrogen atom, and either removal or addition of a further hydrogen atom. Comparison of the values obtained for the two

octenes examined shows a slight but reproducible difference in deuteration depending on the position of the double bond, suggesting that its presence may not be the sole factor determining the extent of deuteration.

TABLE 1. *Comparative deuterations.*

Compound	Relative no. of D atoms introduced into product		Relative no. of D atoms introduced into methyl group of acetic acid solvent	
	Catalyst I	Catalyst II	Catalyst I	Catalyst II
*cyclo*Hexane	0·121	0·027	0·802	0·775
n-Hexane	0·187	0·133	1·02	0·836
*cyclo*Hexanol	0·534	0·209	0·224	0·203
*cyclo*Hexa-1 : 3-diene	0·635	0·473	0·346	0·618
Pent-1-ene	0·980	0·458	0·945	0·588
Oct-2-ene	1·01	0·717	0·702	0·668
Oct-1-ene	1·13	0·885	0·798	0·548
*cyclo*Hexa-1 : 4-diene	2·70	2·37	0·165	0·347
Benzene	2·74	2·73	0·132	0·224
*cyclo*Hexene	2·76	2·87	0·120	0·399

Consideration of the relatively large amounts of deuterium found in the products in the cases of *cyclo*hexene and *cyclo*hexa-1 : 4-diene suggested that here the reaction took place in two steps—a disproportionation reaction resulting in the production of *cyclo*hexane and benzene, followed by the deuteration of the latter hydrocarbon which was shown to exchange extensively under the conditions of these experiments. Comparison of boiling ranges before and after deuteration, and estimation, by titration, of the number of ethylenic bonds present (Table 2) indicated that such disproportionation had occurred. Zelinsky

TABLE 2. *Boiling ranges and double-bond estimations.*

	Boiling range :		Double-bond content after deuteration
	before deuteration	after deuteration	
*cyclo*Hexene	83—84·5°	77·5—78·5°	0·01
	83—84·5	77—79	0·18
*cyclo*Hexa-1 : 4-diene	87	77—78	0·10
	87	77—78	0·04
*cyclo*Hexa-1 : 3-diene	83—86	80—84	0·56
	83—86	80—84	0·59

and Pavlow (*Ber.*, 1924, **56**, 1066; 1925, **58**, 185; cf. Corson and Ipatieff, *J. Amer. Chem. Soc.*, 1939, **61**, 1056; Taylor and Turkevitch, *Trans. Faraday Soc.*, 1939, **35**, 921) showed that *cyclo*hexene, when passed over a palladium catalyst at temperatures between 92° and 230°, isomerised according to the equation :

$$3C_6H_{10} = 2C_6H_{12} + C_6H_6$$

On the assumption that benzene and *cyclo*hexane had been formed in these proportions and by use of the values obtained separately for these hydrocarbons, calculation has shown that if the disproportionation took place independently as a first stage and was followed by deuteration of the resulting *cyclo*hexane and benzene the value for the deuterium content of the mixed products would not be more than 5%. If, however, conversion of the *cyclo*hexene into *cyclo*hexane proceeded by addition of hydrogen in equilibrium with the deuterium present in the solvent the calculated deuterium content would be raised to 7·5%, a value approximating more closely to the experimentally determined value of 8%.

Similar considerations apply to the case of *cyclo*hexa-1 : 4-diene. Here (cf. Zelinsky and Pavlow, *Ber.*, 1933, **66**, 1420) the disproportionation might be represented by the equation :

$$3C_6H_8 = C_6H_6 + 2C_6H_{12}$$

Calculation showed that random addition of deuterium and hydrogen atoms from the solvent to *cyclo*hexadiene would produce a deuterium content in the *cyclo*hexane of 13·9%. The *cyclo*hexane was separated in this case and the atom % of deuterium found to be 11·70.

The fall of the bromine absorption of *cyclo*hexa-1 : 3-diene to a value corresponding to about 0·5 double bond on treatment with palladium had been noted by Zelinsky and Pavlow (*loc. cit.*), who suggested the reactions

$$2C_6H_8 = C_6H_6 + C_6H_{10} \text{ (rapid)}$$

followed by

$$3C_6H_{10} = C_6H_6 + 2C_6H_{12} \text{ (slow)}$$

The comparatively low results obtained in the experiments with the 1 : 3-diene do not appear to be in conformity with this mechanism which would require more extensive deuteration of the products.

The small but significant changes in the boiling ranges of the samples of the octenes seem to indicate that some isomerisation may have occurred.

Of the exchange reactions reported in this paper those affording maximum deuteration of the products involved either a platinum-catalysed exchange reaction between benzene and deuterium oxide or a platinum-catalysed disproportionation occurring in deuterium oxide. To the established classes of exchange reactions involving ionisable hydrogen atoms, incipiently ionised hydrogen atoms or tautomeric changes, might therefore be added deuterations accompanying disproportionation or isomerisation in heavy water induced by heterogeneous catalysis.

Experimental

Deuterations.—All deuterations were carried out in presence of a platinum black catalyst in a medium of acetic acid and heavy water. The purified reactants were weighed into Pyrex tubes in quantities shown in Table 3, the weights of hydrocarbons being in approximately equimolecular proportions.

After being charged, the tubes were cooled in liquid air, evacuated, sealed, and shaken for 3 days at 123—133°.

Table 3. *Contents of reaction tubes : boiling ranges before and after deuteration.*

	Compound (g.)	Catalyst (g.)	D_2O (g.)	AcOH (g.)	Boiling range: starting material	Boiling range: product
Catalyst I						
n-Hexane	3·106	0·0805	0·427	1·635	68°	67—68°
*cyclo*Hexane	3·011	0·0810	0·427	1·636	80—80·2	80
*cyclo*Hexanol	2·934	0·0810	0·433	1·653	161	158—160
*cyclo*Hexene *	2·973	0·0810	0·435	1·645	83—84·5	77·8—78·5
Pent-1-ene	2·567	0·0810	0·429	1·641	38—39	38—39
Oct-1-ene	3·977	0·0810	0·433	1·651	119—121	120—122·5
Oct-2-ene	3·976	0·0810	0·431	1·644	122—124·5	123—124·5
*cyclo*Hexa-1 : 4-diene *	2·841	0·0810	0·434	1·640	87	77—78
*cyclo*Hexa-1 : 3-diene *	2·855	0·0810	0·437	1·651	83—86	80—84
Benzene	2·771	0·0810	0·434	1·640	80—80·5	78
Catalyst II						
n-Hexane	3·128	0·0810	0·431	1·646	68	67—68
*cyclo*Hexane	3·034	0·0810	0·432	1·648	80—80·2	80—80·5
*cyclo*Hexanol	3·017	0·0810	0·439	1·674	161	160—163
*cyclo*Hexene *	2·989	0·0810	0·434	1·653	83—84·5	77—79
Pent-1-ene	2·583	0·0810	0·433	1·654	38—39	37—39
Oct-1-ene	3·977	0·0810	0·432	1·651	120—121	120—122
Oct-2-ene	3·973	0·0810	0·431	1·648	123·5—125	122—124
*cyclo*Hexa-1 : 4-diene *	2·853	0·0810	0·431	1·643	87	77—78
*cyclo*Hexa-1 : 3-diene *	2·833	0·0810	0·432	1·646	83—86	80—84
Benzene	2·790	0·0810	0·432	1·647	80—80·5	77

* Disproportionation of the hydrocarbon took place.

Isolation of the Products.—The reaction tubes were cooled in liquid air and opened. Where possible, the two layers of liquid were separated and the hydrocarbons dried and freed from traces of acid with solid sodium hydroxide. The hydrocarbons were distilled and the ranges over which they boiled observed : in a few cases, some drops of a higher-boiling, coloured liquid remained. The residues contained considerably more deuterium than the parent hydrocarbons.

The *cyclo*hexanol samples required a different method of separation as the product in the reaction tube was homogeneous and probably contained some *cyclo*hexyl acetate. After removal of the catalyst this liquid was refluxed for 3 hours with aqueous sodium hydroxide (3 g. in 25 ml. of water), and the *cyclo*hexanol recovered by ether-extraction.

The products from the *cyclo*hexadienes were washed with water and dried ($CaCl_2$) to avoid the possibility of polymerisation. The only losses occurring were due to the slight solubility of the hydrocarbons in the acetic acid–water mixture and also to the minute quantities of polymer formed.

The acetic acid–water solvent from each reaction mixture was converted into silver acetate by the addition of aqueous acetic acid to a 30% excess of silver oxide, a quantity known to produce 99·9% conversion into silver acetate. The silver acetate was recovered by crystallisation from water after removal of the excess of silver oxide. Investigation showed that this recovery process caused negligible loss of deuterium from the methyl group of the acetic acid.

Isolation of the acetic acid from the *cyclo*hexanol deuteration involved steam-distillation of the acidified aqueous layer after ether-extraction of the *cyclo*hexanol. The acetic acid was converted into silver acetate by the method indicated above.

Preparation of Reactants.—Acetic acid. " AnalaR " acid was refluxed with chromium trioxide and purified by distillation and crystallisation.

Heavy water. " Norsk Hydro " product of 99·75% deuterium oxide by weight was used.

cyclo*Hexane*, n-*hexane*, cyclo*hexene*, *oct*-1-*ene*, *and oct*-2-*ene*. These were purified by distillation.

cyclo*Hexanol*. This was shaken with aqueous alkali, washed with water, dried (K_2CO_3), and distilled.

Pent-1-*ene*. *n*-Amyl alcohol was dehydrated with sulphuric acid (Adams, Kamm, and Marvel, *J. Amer. Chem. Soc.*, 1918, **40**, 1950). The product was fractionated in a Widmer column.

cyclo*Hexa*-1 : 4-*diene*. Quinol was hydrogenated under pressure with Raney nickel (Adkins and Cramer, *J. Amer. Chem. Soc.*, 1930, **52**, 4349). The diol produced was dehydrated with concentrated sulphuric acid, and the product fractionated in a Widmer column (Senderens, *Compt. rend.*, 1923, 1183).

cyclo*Hexa*-1 : 3-*diene*. 1 : 2-Dibromo*cyclo*hexane was prepared by bromination of *cyclo*hexene (*Org. Synth.*, Coll. Vol. II, Wiley, 1943, p. 171). Dehydrobromination was accomplished by boiling the dibromide in quinoline (Zelinsky and Gorsky, *Ber.*, 1908, **41**, 2479).

Benzene. " Crystallisable " benzene was shaken several times with concentrated sulphuric acid, washed with water, dried, crystallised, and distilled.

Platinum black on asbestos catalyst. Formaldehyde reduction of a platinum salt solution containing a suspension of purified asbestos produced the catalyst (Vogel, " Textbook of Practical Organic Chemistry," Longmans, 1948, p. 842, Method A).

Separation of the Saturated Disproportionation Product of cyclo*Hexa*-1 : 4-*diene*.—A portion of the product (1·11 g.) from the reaction mixture was treated with 30% oleum (an equal volume), and the mixture set aside for 15 minutes at room temperature. The unchanged hydrocarbon was separated after dilution of the mixture with water. This portion was assumed to be *cyclo*hexane and was washed with water and dried ($CaCl_2$) (yield, 0·05 g.).

Refractive Index Measurements on the Products of cyclo*Hexene Disproportionation*.—Zelinsky and Pavlow (*Ber.*, 1924, **57**, 1066; 1925, **58**, 185) observed that passage of *cyclo*hexene over palladium at 164° and 223° gave products of n_D^{20} 1·4448 and 1·4489 respectively. These values they compared with a 1 : 2 benzene–*cyclo*hexane mixture with n_D^{20} 1·4455. Measurements on the *cyclo*hexene before deuteration gave n_D^{18} 1·4484 and on the products after deuteration n_D^{18} 1·4422.

Estimation of Deuterium.—The water produced by combustion of the deuterio-compounds in air or oxygen was purified by a modification of the method used by Keston, Rittenberg, and Schoenheimer (*J. Biol. Chem.*, 1937, **122**, 227), and the deuterium content of the water measured by the " Gradient Tube " method (Linderstrøm-Lang, Jacobsen, and Johansen, *Compt. rend. Trav. Lab., Carlsberg*, 1938, **23**, 17; Linderstrøm-Lang and Lanz, *ibid.*, 1938, **21**, 315).

We thank Mr. Angus Macdonald for the deuterium assays. Our thanks are also offered to the Department of Scientific and Industrial Research for a Maintenance Allowance to one of us (S. J. T.), during the tenure of which part of this work was completed.

THE UNIVERSITY, GLASGOW, W.2. [*Received, September 22nd*, 1951.]

102. *The Catalytic Deuteration of Organic Compounds. Part II.* The Deuteration of Cholesterol and Ergosterol.*

By J. Bell and S. J. Thomson.

Deuteriocholesterol and deuterioergosterol have been prepared under comparable experimental conditions by Bloch and Rittenberg's method, *i.e.*, a platinum-catalysed exchange reaction between the sterols and deuterium oxide. A reaction involving the migration of double bonds has been shown to occur, by the isolation of deuteriocholest-4-en-3-one and deuterioergosterol B_1, in cholesterol and ergosterol deuterations respectively. The role of the solvent, acetic acid and deuterium oxide, has been studied, and the possibility of the deuteration of the acetic acid in the methyl group being an essential preliminary to sterol deuteration has been eliminated. The deuteration of cholesterol by use of an acid other than acetic together with a platinum catalyst was unsuccessful.

Deuteriocholesterol and deuterioergosterol have been prepared under comparable experimental conditions by Bloch and Rittenbergs's method (*J. Biol. Chem.*, 1943, **149**, 505), the sterols being shaken for three days at 123—133° in sealed evacuated tubes containing heavy water, acetic acid, and Adams's platinum catalyst. By this means deuterium was introduced into the sterols and the methyl group of the acetic acid solvent. In accordance with Bloch and Rittenberg's work considerable destruction of the sterols was observed.

The annexed Table shows the extent of these deuteration reactions for various quantities of Adams's catalyst.

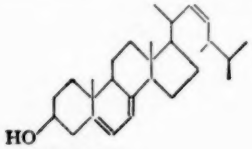
Deuteration of ergosterol and cholesterol.

	Cholesterol			Ergosterol		
Experiment	1A	2A	3A	1B	2B	3B
G. of Pt per g. of sterol	0·1218	0·2352	0·3582	0·1263	0·2343	0·3631
Atom % deuterium in sterol	1·36	1·48	2·12	0·93	2·66	2·79
Atom % deuterium in methyl group of acetic acid solvent	3·06	3·65	4·12	2·30	3·43	7·83

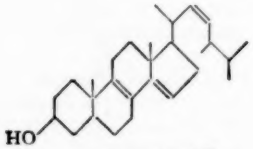
Consideration of these reactions in the light of the information gained in Part I,* suggested that those parts of the sterol molecule containing only saturated carbon chains would contain little deuterium, whereas greater deuteration would occur in the vicinity of the hydroxyl group and the double bonds.

The increased deuteration of ergosterol as shown in Experiments 2 and 3 might be attributed to the conjugated double bonds of ring B and the double bond of the side chain.

It had been observed in Part I that considerable exchange had occurred together with a disproportionation reaction. This could be explained by assuming that, under the influence of the catalyst, hydrogen was removed from some molecules and deuterium or hydrogen from the solvent added to others.



Ergosterol



Ergosterol B_1

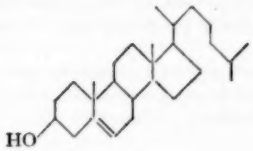
Some such process might be operative in the deuteration of sterols containing double bonds. A reaction similar to the disproportionation would be the removal of hydrogen from a ring of the sterol molecule and the addition of hydrogen or deuterium to the double bond position, the removal and addition reactions taking place in either this or the reverse

* Part I, preceding paper.

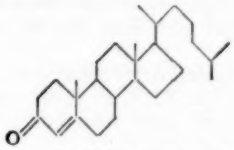
order. This would result in the migration of double bonds in the sterol rings and the consequent production of isomers containing relatively large amounts of deuterium.

The isolation of deuterioergosteryl B_1 acetate on treatment of ergosterol with deuterium oxide, acetic acid, and a platinum-black-on-asbestos catalyst showed that double-bond migration had occurred. Furthermore, the sterol portion of the ester contained 3·68 atom % of deuterium, probably in the 5, 6, and 7 positions.

Similar treatment of cholesterol yielded cholest-4-en-3-one containing 0·21 atom % of deuterium. Again double-bond migration had occurred together with deuteration. In this case the parent sterol was isolated and was found to contain 0·12 atom % of deuterium.



Cholesterol



Cholest-4-en-3-one

This type of side reaction may have accounted for some of the destruction of the sterol during deuteration recorded by Bloch and Rittenberg and earlier in this paper.

Since deuteriocholest-4-en-3-one was produced during the deuteration of cholesterol it seemed not unreasonable to examine positions 3 and 4 of the deuteriocholesterol for deuterium atoms. This was accomplished by converting a sample of the deuteriocholesterol into cholest-4-en-3-one, thereby removing some of the deuterium or hydrogen atoms from positions 3 and 4. The atom % of deuterium in both cholesterol and the resultant cholest-4-en-3-one was 0·12. It must be concluded that the deuteriocholesterol did not contain deuterium in position 3 or 4.

During the deuteration of ergosterol and cholesterol the deuterio-isomerisation products were isolated in small yields. Such deuterations by isomerisation in heavy water might, however, be extended to the preparation of deuterio-organic compounds normally produced in reasonable yields by isomerisation reactions.

From the results shown in Part I, Table 1, and in Part II (p. 576), it will be seen that in all cases deuterium was introduced into the methyl group of the acetic acid, in conformity with the observation made in the course of this work that relatively large amounts of deuterium could be introduced into acetic acid by similar treatment with heavy water in presence of catalysts.

The function of the acetic acid appeared to be not only that of solvent, since an attempted deuteration of cholesterol with heavy water, a platinum catalyst, and dilute sulphuric acid in alcohol failed. Only very small quantities of deuterium were introduced into the sterol product by treatment of ergosterol with anhydrous deuterioacetic acid (with deuterium atoms in the methyl group only), indicating that the production of the deuterio-acid is unlikely to be an essential preliminary to the deuteration of the sterol.

Experimental

Preparation of Deuterio-cholesterol and -ergosterol.—Acetic acid, heavy water, and platinum oxide (Adams's catalyst) in the quantities shown in the Table below were weighed into 6″ × ½″ tubes. Hydrogen was passed into the suspension for 90 minutes, followed by nitrogen for 60 minutes to remove as much of the hydrogen as possible. The weighed quantities of the sterols were added and the contents of the tube frozen. After evacuation and sealing, the tubes were shaken for 3 days at 123—133°.

Expt.	Sterol (g.)	D_2O (g.)	H_2O (g.)	AcOH (g.)	PtO_2,H_2O (g.)
i, E_1	0·7975	0·6650	0·1515	2·8060	0·1270
C_1	0·7945	0·6490	0·2090	2·7850	0·1220
ii, E_2	0·7850	0·6975	0·2075	2·7460	0·2320
C_2	0·7925	0·6680	0·2045	2·7345	0·2355
iii, E_3	0·7870	0·6480	0·2040	2·7450	0·3600
C_3	0·7970	0·6520	0·2055	2·7180	0·3600

Recovery of the Sterols.—The acetic acid and water were recovered by vacuum-distillation, the residues from the distillation were warmed with ether, and the catalyst was filtered off. The filtrate was evaporated to dryness, and the steryl acetates were hydrolysed with alcoholic potassium hydroxide. The cholesteryl acetate was refluxed for 40 minutes with 40 ml. of 2% solution, and the ergosteryl acetate with 60 ml. of 5% solution. Boiling under reduced pressure and slow evaporation removed the alcohol. The residues were extracted with water and then with ether. The ethereal extracts on evaporation yielded gums which gave crystalline sterols from alcohol, benzene–alcohol, and acetone. In later experiments this process was superseded by chromatographic separation on alumina.

Cholesterol and Ergosterol Chromatography.—The columns were prepared from alumina suspensions in benzene and the sterols added in light petroleum (b. p. 60—80°) solution. The eluants were light petroleum and benzene. The sterols produced were crystallised from dry alcohol.

M. p.s (in a vacuum), mixed m. p.s with the parent sterols, and yields were as follows :

Ergosterol : Expt. E1, m. p. 164·3°, mixed m. p. 163·5° (with ergosterol, m. p. 163·5°), 0·067 g. ; Expt. E2, m. p. 150—151°, mixed m. p. 158—161°, 0·090 g. ; Expt. E3, m. p. 160°, mixed m. p. 163°, 0·029 g.

Cholesterol : Expt. C1, m. p. 145·5°, mixed m. p. 145·5° (with cholesterol, m. p. 146—147°), 0·090 g. ; Expt. C2, m. p. 142°, mixed m. p. 144—146°, 0·140 g. ; Expt. C3, m. p. 145°, mixed m. p. 146—147°, 0·099 g.

Recovery of Acetic Acid Solvent.—The distillate recovered after the exchange reaction consisted of water and acetic acid. The acid was converted into silver acetate by the method described in Part I.

Starting Materials.—Ergosterol. Commercial ergosterol was purified by Bills and Cox's method (*J. Biol. Chem.*, 1929, **84**, 455) using 2 : 1 alcohol–benzene for crystallisations. After purification, the sterol melted at 163·5° (in a vacuum), and had $[\alpha]_{Hg}^{20}$ −160·2° (*c*, 1% in chloroform).

Cholesterol. Alcohol extraction of gallstones and repeated crystallisations from alcohol gave a product, m. p. 146—147°.

Acetic Acid. This was purified by refluxing it over chromium trioxide, distillation, and crystallisation.

Deuterium oxide. 99·6% by weight, " Norsk Hydro."

Water. Ordinary distilled water was redistilled four times, the first two distillations being from potassium permanganate.

Investigation of the Products in an Attempted Deuteration of Ergosterol.—A platinum-black-on-asbestos catalyst was prepared by formaldehyde reduction of a platinum salt solution (Vogel, " Textbook of Practical Organic Chemistry," Longmans, 1948, p. 824, Method A). Ergosterol {4·804 g. ; m. p. 163·5—164·8° (in a vacuum), $[\alpha]_{Hg}^{18}$ −163·5°}, acetic acid (17·381 g.), water (1·300 g.), deuterium oxide (4·153 g.), and catalyst (0·810 g.) were placed in a " Pyrex " reaction vessel which was then cooled in a freezing mixture, evacuated, sealed, and shaken for 3 days at 124—135°. The tube was cooled and the volatile components removed by vacuum-distillation : 22·291 g. were recovered, leaving 0·543 g. as residue, probably as steryl acetate. The residues were dissolved in chloroform, the catalyst was filtered off, and the filtrate evaporated to a gum and dissolved in benzene. An alumina chromatograph column was moistened with light petroleum (b. p. 60—80°). The benzene solution was added and elution performed with light petroleum (b. p. 60—80°), benzene, chloroform, alcohol, and acetone. Each portion of the eluant was evaporated and the residues obtained were boiled with charcoal in alcohol. Many attempts to crystallise these products were made, using a great variety of methods and solvents. Finally " fraction 10 " yielded crystals from alcohol when the solution (10 ml.) was poured into a vessel containing 0·2 ml. of water. The white crystals obtained, m. p. 131°, crystallised from benzene–alcohol (1 : 4) as small elongated plates, m. p. 135—136·5°, $[\alpha]_D^{18}$ −50·9° in chloroform : the yield of pure material was 0·05 g., $\lambda_{max.}^{CHCl_3}$ 248 mμ (Found : C, 81·9; H, 10·3. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%).

Examination of the other fractions by Windaus's method (*Annalen*, 1931, **488**, 91) suggested that ergosterols B_2 and B_3 were absent. In a second deuteration, ergosterol (5·433 g. ; m. p. 163·5° (*in vacuo*), $[\alpha]_{Hg}^{19}$ −166·4° in chloroform), acetic acid (17·230 g.), water (1·295 g.), deuterium oxide (4·288 g.), and catalyst (0·810 g.) were shaken as before for 3 days at 125—129° ; 21·500 g. of solvent were recovered. The solids remaining were dissolved in hot alcohol, charcoal was added, and the catalyst and charcoal were filtered off. The filtrate was placed in a refrigerator and a crop of crystals collected, having m. p. 128—131°. Two further crops, collected similarly by

reduction of the volume of alcohol, had m. p. 125° and 124·5° respectively. These three samples were combined (1·15 g.) and many crystallisations from alcohol yielded a product (0·50 g.), m. p. 139·5—141°, $[\alpha]_D^{18\cdot5}$ −56·1° in chloroform, $\lambda_{max.}^{ether}$ 249 mμ (Found: C, 82·3; H, 10·3%) (cf. Windaus, m. p. 142°, $[\alpha]_D^{19}$ −53·6°, $\lambda_{max.}$ for ergosterol B_1 248 mμ in ether).

Deuteration of Cholesterol.—Starting materials. The water, acetic acid, and platinum catalyst were from stocks prepared for the previous experiments. The deuterium oxide (" Norsk Hydro ") was 99·6% by weight.

Cholesterol (10·580 g.), acetic acid (33·832 g.), water (2·675 g.), deuterium oxide (8·960 g.), and catalyst (1·447 g.) were shaken as before for 3 days at 125—129°. The acetic acid and water were recovered by vacuum-distillation, and the acid was converted into silver acetate. The residues were dissolved in hot alcohol, and the catalyst was filtered off. An alumina column for chromatographic analysis was prepared and moistened with carbon tetrachloride. The sterol products were added in a solution of the same solvent. Elution was by carbon tetrachloride, and by 0·1, 0·2, 0·5, 1, 2, 5, 10, 50, and 100% alcohol in carbon tetrachloride.

The twenty-five fractions so obtained were evaporated and attempts made to crystallise the residues. Gums or oils were obtained from all fractions with the exception of the following:

Fraction 4: Crystallisations from methyl alcohol and acetone mixtures, followed by ethyl alcohol, yielded cholesteryl acetate (0·21 g.), m. p. 114·5° $[\alpha]_D^{19}$ −40·5° in chloroform.

Fractions 7—12: Methyl alcohol crystallisations yielded cholest-4-en-3-one (0·3 g.), m. p. 80°, $[\alpha]_D^{19}$ + 86·7° in chloroform, $\lambda_{max.}^{ether}$ 234 mμ; it gave a semicarbazone, m. p. 231° (decomp.) (Found: C, 76·1; H, 10·5; N, 9·7. Calc. for $C_{28}H_{47}ON_3$: C, 76·1; H, 10·7; N, 9·5%).

Fraction 14: Ethyl alcohol crystallisations yielded cholesterol (0·55 g.), m. p. 147·5°, $[\alpha]_D^{20}$ −40·0° in chloroform.

Location of Deuterium Atoms in Deuteriocholesterol. Conversion of Deuteriocholesterol into Cholest-4-en-3-one.—Bromination (Windaus, *Ber.*, 1906, **39**, 518). Deuteriocholesterol (0·464 g.) was dissolved in ether (4·6 ml.), and a solution of bromine in acetic acid added (2·32 ml. of a solution of 2·032 g. of bromine in 21·135 g. of glacial acetic acid). The mixed liquids set to a solid yellowish mass almost at once and this was stirred with diluted acetic acid (3 : 1 acetic acid : water), filtered, washed with water, and dried in a vacuum.

Oxidation of cholesterol dibromide (Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407). The dibromide (0·65 g.) was dissolved in benzene (6·5 ml.), and a solution of chromium trioxide in aqueous acetic acid added (6·5 ml. of a solution of 1·2 g. of chromium trioxide in 12 ml. of water and 24 ml. of acetic acid). The liquids were shaken together for 6 hours at room temperature, and the benzene layer was separated and washed with water until neutral to litmus. After being dried (Na_2SO_4), the benzene was evaporated off, leaving a residue of 5 : 6-dibromocholestan-3-one.

Debromination (Butenandt and Schmidt-Thomé, *Ber.*, 1936, **69**, 882). The cholestanone dibromide (0·3 g.) was dissolved in a mixture of ethyl alcohol (10 ml.) and methyl alcohol (10 ml.), and zinc dust (0·3 g.) was added with dilute sulphuric acid (0·8 ml. of 4N-acid). The suspension was boiled for 10 minutes and filtered, and the alcohol removed from the filtrate under vacuum. The residue was crystallised four times from methyl alcohol. The product was cholest-4-en-3-one (0·11 g.), m. p. 79·5°.

Attempted Deuteration of Cholesterol with Deuterium Oxide, a Platinum Catalyst, and Dilute Sulphuric Acid in Alcohol.—Adams's catalyst (0·393 g.) was weighed into alcohol, and hydrogen passed in for 1 hour to reduce the catalyst to its active form. Nitrogen, to remove as much hydrogen as possible, was passed through the suspension for 2 hours. The weight of alcohol was made up to 9·544 g., and deuterium oxide (2·211 g.; 99·6% by weight, " Norsk Hydro "), sulphuric acid (1·090 g. of 4N-acid), and cholesterol (2·547 g. of a sample, m. p. 148·5—149°, $[\alpha]_D^{20}$ −39·5°) were added. This mixture was refluxed on a steam-bath for 26 hours. Hot alcohol was added and the catalyst filtered off. Crystals separated from the filtrate on cooling. Crystallised from alcohol, these (1·2 g.) had m. p. 148°.

Deuteration of Ergosterol with Glacial Deuterioacetic Acid and a Platinum Catalyst.—Preparation of the acid. Acetic acid (1·04 g.), deuterium oxide (0·55 g.; 99·8% by weight), and platinum-black-on-asbestos catalyst (0·05 g.) were shaken for 3 days at 123—133°, in a sealed evacuated tube. The acid was isolated as the silver salt. Silver deuterioacetate (12·3 g.) was refluxed for 20 minutes with syrupy phosphoric acid (16 ml.). The mixture was then distilled and the acetic acid boiling at 115—116° collected. 4 Ml. of ordinary acetic acid were added to the 2 ml. of deuterioacetic acid; the mixture had m.p. 7°, *i.e.*, 93·4% acetic acid (6·6% H_2O). This mixture was dehydrated by refluxing it with triacetyl borate (4·2 g.) (Pictet and Geleznoff, *Ber.*, 1903, **36**, 2219) for 4 hours. The acid produced by distillation melted at 16°. This treat-

ment with triacetyl borate was repeated twice more, 0·7 g. being used each time. The product melted at 16·9°. The volume of glacial deuterioacetic acid was 7·5 ml. A few ml. of this acid were converted into silver acetate for deuterium estimation.

Deuteration. Glacial deuterioacetic acid (3·165 g.), a platinum-black-on-asbestos catalyst (0·622 g.), and ergosterol (0·792 g. of a sample, m. p. 163·5°, $[\alpha]_{Hg}^{20}$ −160·2° in chloroform) were shaken for 3 days at 123—133°. The acid was distilled off under reduced pressure and converted into silver acetate. The sterol residue was dissolved in ether, and the catalyst filtered off. The residue obtained on evaporation of the ether was hydrolysed with alcoholic potassium hydroxide (2·5 g. in 2 ml. of water and 50 ml. of alcohol). The alcohol was removed under a vacuum and the residue extracted with water. The sterol portion was then dried and dissolved in light petroleum (b. p. 40—60°; 80 ml.)–benzene (10 ml.). This solution was then added to an alumina chromatograph column moistened with benzene. Elution was with light petroleum (b. p. 40—60°), followed by benzene and benzene–alcohol (1 : 4 by volume).

Oils and gums were obtained from the chromatograph with some white solid. This was crystallised from alcohol many times and finally had m. p. 142° in a vacuum. Further crystallisation from benzene–alcohol (1 : 2 by volume) yielded 0·089 g. of a product, m. p. 145°, $[\alpha]_D$ −63·5° in chloroform, probably impure ergosterol B_1 mixed with the original sterol (ergosterol B_1, m. p. 148°, $[\alpha]_D$ −40°).

Deuterium contents. Atom % deuterium in methyl group of acetic acid before deuteration, 1·65. After deuteration, 1·63. Atom % deuterium in sterol, 0·17.

We thank Miss R. H. Kennaway and Mr. J. M. L. Cameron for the microanalyses, and Mr. Angus Macdonald for the deuterium assays. Our thanks are also due to the Department of Scientific and Industrial Research for a Maintenance Allowance to one of us (S. J. T.) during the tenure of which part of this work was completed.

THE UNIVERSITY, GLASGOW, W.2. [*Received, September 22nd,* 1951.]

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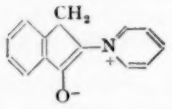
103. *Two Enol Betaines of the Indane-pyridinium Series.*

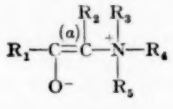
By W. H. STAFFORD.

The syntheses and properties of the enol betaines (I) and (IV) derived from pyridine and indan-1-one and indane-1 : 3-dione respectively are described.

THE enol betaine (I) was obtained as an orange, crystalline hydrate by the action of dilute sodium hydroxide on an aqueous solution of 1-(3-hydroxyinden-2-yl)pyridinium bromide. The first evidence for the existence of compounds of the general enol betaine structure (II) was presented by Krollpfeiffer and Müller (*Ber.*, 1933, **66**, 739) who had isolated reactive, orange-coloured, highly crystalline compounds as intermediates in the "acid cleavage" of pyridinium salts derived from alkyl *o*-α-halogenoacylphenyl sulphides. This structure was subsequently confirmed by Kröhnke (*Ber.*, 1935, **68**, 1177) for the simpler product (III) from phenacylpyridinium bromide and in many subsequent papers for enol betaines in which R_2 = H, alkyl, or acyl. Although the reactions of these compounds have been exhaustively examined, their physical properties have been largely ignored.



(I)



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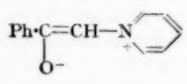
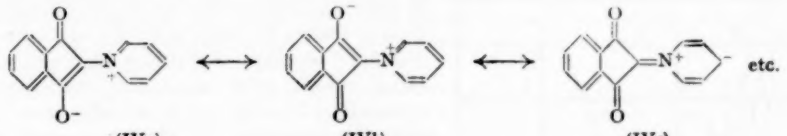


(III)

Crystallisation of the enol betaine (I) from aqueous methanol or ethanol under a variety of conditions gave a series of hydrates whose colour became less intense as the degree of hydration increased (cf. Kröhnke, *loc. cit.*; Kröhnke and Kübler, *Ber.*, 1937, **70**, 538). The problem of facile changes in hydration, combined with sensitivity to light, made reliable analyses difficult to obtain (cf. Krollpfeiffer and Müller, *Ber.*, 1935, **68**, 1169). The betaine

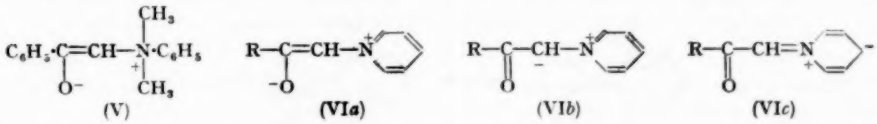
is soluble in ethanol, methanol, and to a lesser extent in water; it is only very slightly soluble in solvents such as benzene, chloroform, and ether. Solutions in ethanol are red when concentrated and yellow when dilute and do not fluoresce in ultra-violet light. The enol betaine is quite strongly basic and dissolves readily in dilute acetic acid and mineral acids, giving colourless solutions which fluoresce green in ultra-violet light. It may be recovered from acid solutions by making them slightly alkaline with caustic alkali. Specimens exposed to light darken quickly and solutions of these in acids are then slightly coloured ; this may be due to photo-oxidation. Oxidation of the betaine with hydrogen peroxide yielded homophthalic acid (cf. Krollpfeiffer and Müller, *loc. cit.*).



(IV*a*) (IV*b*) (IV*c*)

The enol betaine (IV) from indane-1 : 3-dione was obtained directly by the action of alkali on the water-soluble product from the bromination of indane-1 : 3-dione in pyridine solution. Presumably bromination of the diketone (cf. Vona and Merker, *J. Org. Chem.*, 1949, **14**, 1048) was followed by the formation of the water-soluble pyridinium bromide by reaction with excess of pyridine (cf. King, McWhirter, and Rowland, *J. Amer. Chem. Soc.*, 1948, **70**, 239). This enol betaine was more soluble in non-polar solvents and was much more stable than was (I). It was recrystallised from methanol or aqueous ethanol and from the latter it showed no tendency to crystallise as a hydrate.

Although Kröhnke realised that the colour of the enol betaine could only be explained from the combination of the extended conjugated system and the polar nature of the molecule he made no deeper analysis of the problem. He did not, for example, attempt to explain the great difference in colour between the pyridinium enol betaine (III) and the anilinium enol betaine (V)—the latter is colourless. In the acylpyridinium enol betaines it seems reasonable to assume that, besides the two canonical forms (VI*a*) and (VI*b*), others, *e.g.*, (VI*c*), must contribute. The betaine (V) has two contributing structures



(V) (VI*a*) (VI*b*) (VI*c*)

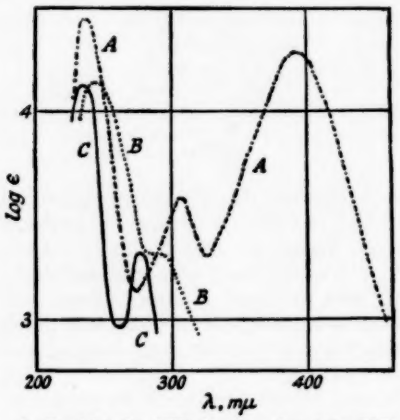
analogous to (VI*a* and *b*), but no contributing structures involving charge separation in the nitrogen-containing moiety are possible. This restriction in resonance is probably responsible for the differences in colour. The relative contributions of these various canonical forms are probably also responsible for the differences in colour and stability observed by Kröhnke in the phenacyl-pyridinium, -picolinium, -quinolinium, and -*iso*quinolinium series.

The absorption spectra of (I) in alcohol, water, and 0·1N-hydrochloric acid were determined. Extremely large discrepancies from the Lambert–Beer law were observed for alcoholic and, to a smaller extent, aqueous solutions. This was due to photochemical decomposition during the exposure to the arc—the solutions, initially yellow, rapidly faded . No reliance could therefore be placed on the values of log $\varepsilon_{max.}$ but the wave-lengths of the maxima were quite reproducible, *viz.*, 425 and 257 mμ in water, and 440 and 252 mμ in alcohol. The bathochromic shift for the absorption band in the visible region on change of solvent from water to ethanol is analogous to the change in the depth of colour of the hydrated crystals on alteration of the degree of hydration. The molecular environment in the crystal and in solution must affect the colour, probably by altering the effective contributions of the various dipolar canonical forms owing to differences in the dielectric

constant of the solvent or surroundings, the polarity of neighbouring molecules, or the susceptibility to induction or mutual induction of dipoles in neighbouring molecules.

In solution in dilute hydrochloric acid the enol betaine has an entirely different absorption spectrum (see figure). It is presumably the absorption spectrum of 1-(3-hydroxyinden-2-yl)pyridinium chloride, and comparison with the absorption spectrum of indan-1-one (Ramart-Lucas and Hoch, *Bull. Soc. chim.*, 1935, **2**, 333) shows a reasonable similarity in form with a bathochromic shift.

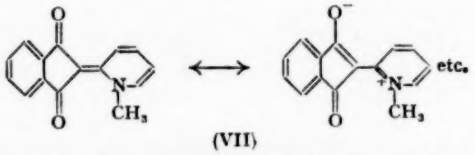
The enol betaine (IV) is stable to ultra-violet light, and in ethanol solution has three prominent maxima and two minima (see figure). No change in absorption is observed in water or hydrochloric acid (N/10). Unlike (I), it does not react with mercuric chloride, a fact clearly shown by the absorption spectrum of an ethanolic solution containing mercuric chloride (1%), which gave an absorption curve substantially the same as in ethanol alone except that the maximum at 238·5 mμ could not be observed owing to the complete absorption by the mercuric chloride below 270 mμ.



A, Enol betaine (IV) *in ethanol or* 0·1N-HCl.
B, Enol betaine (I) *in dil.* HCl.
C, Indan-1-one in ethanol.

The enol betaine (IV), like other α-acyl enol betaines is capable of the mesomerism indicated by (IV*a* and *b*). This possibility was clearly recognised by Kröhnke in the case of related compounds, and the diminished basicity is indicative of the existence of this resonance. In addition, other dipolar structures, *e.g.* (IV*c*), must contribute. An interesting comparison can be made between this enol betaine and "*N*-methylpyrophthalone" (VII) (Kuhn and Bär, *Annalen*, 1935, **516**, 158), some of whose contributing structures are enol betaines.

In many recent papers on "meso-ionic" compounds (Baker *et al.*, *J.*, 1949, **307**, etc.) certain compounds whose structure could only be represented as a hybrid of several ionic forms, dipolar in nature, have been discussed but Kröhnke and Krollpfeiffer's enol betaines



(VII)

have not been mentioned. The sydnones and related meso-ionic compounds are in fact enol betaines in so far as their principal contributing structures contain the general enol betaine structure (II) (cf. Hill and Sutton, *J.*, 1949, **452**). The agreement between the proposed mechanisms of sydnone and enol betaine formation is also apparent, for both involve the removal of a hydrogen ion, in the former case by an acetate ion and in the latter by a hydroxyl ion (Baker *et al.*, *J.*, 1950, **1544**).

Experimental

Absorption spectra were determined with a Hilger Barfit medium spectrograph.

1-(3-*Hydroxyinden-2-yl*)*pyridinium Hydroxide Anhydro-salt*,* *the Enol Betaine* (I).—2-Bromoindan-1-one (2·1 g.) in dry pyridine (5 ml.) was boiled for 1 minute. The brown opaque mixture resulting was taken up in water, and the excess of pyridine was removed by ether-extraction. The aqueous layer was made alkaline with cold sodium hydroxide solution (2N). Immediate separation of orange needles (1·7 g.) occurred. Recrystallisation from 90% methanol gave the enol betaine as irregular, red, rhombic prisms of the *hemihydrate* [Found: C, 76·4;

* For this nomenclature, cf. *J.*, 1950, 630.

H, 5·6; N, 5·8. $(C_{14}H_{11}ON)_2,H_2O$ requires C, 77·0; H, 5·5; N, 6·4%). Recrystallisation from 30% aqueous methanol gave slender orange needles of a *dihydrate* (Found: C, 68·9; H, 5·6. $C_{14}H_{11}ON,2H_2O$ requires C, 68·6; H, 6·2%). These hydrates lost water when heated above 100° and darkening occurred. Above 150° decomposition was apparent and the m. p. was dependent on the rate of heating, 170° being the highest value obtained (by rapid heating).

The enol betaine (0·1 g.) was oxidised by alkaline hydrogen peroxide (2 ml.; 0·5N-sodium hydroxide containing 10% of peroxide), to give a colourless solution; acidification after 24 hours gave homophthalic acid (0·035 g.), m. p. 180—181° (lit., 183°) alone or mixed with authentic material (Found: C, 59·5; H, 4·5. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5%).

The betaine formed an extremely insoluble, colourless mercurichloride which could not be purified as digestion with warm solvents caused decomposition to an insoluble coloured mass. The extreme insolubility was shown by mixing equal volumes of ethanolic solutions of the betaine (M/5000) and mercuric chloride (1%). An opacity followed by rapid coagulation leaving a colourless supernatant fluid occurred.

1-(1-*Keto*-3-*hydroxyinden*-2-*yl*)*pyridinium Hydroxide Anhydro-salt, the Enol Betaine* (IV).—A solution of bromine (0·75 ml.) in pyridine (5 ml.) was added to indane-1 : 3-dione (1·46 g.) in pyridine (2 ml.). After a few minutes' warming the solution was poured into water (100 ml.). The excess of pyridine was extracted with ether, and the coloured aqueous layer was made alkaline with 2N-sodium hydroxide. The dark solution slowly deposited the *enol betaine* as elongated yellow plates which crystallised from ethanol as elongated prisms (0·5 g.) with a yellow, metallic lustre, m. p. 255—256° (decomp.) (Found: C, 74·5; H, 3·9; N, 6·2. $C_{14}H_9O_2N$ requires C, 75·3; H, 4·1; N, 6·3%).

Thanks are offered to the Carnegie Trust for the Universities of Scotland for a Scholarship and to N. Keir for assistance in the Laboratory.

THE UNIVERSITY OF EDINBURGH. [*Received, October* 1*st*, 1951.]

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104. *Experiments on the Preparation of Certain Derivatives of 2- and 4-Benzylpyridine.*

By A. J. NUNN and K. SCHOFIELD.

Satisfactory conditions for the preparation of certain nitro- and amino-derivatives of 2- and 4-benzyl- and -benzoyl-pyridine are described. The use of copper sulphate as a catalyst in deaminations utilising hypophosphorous acid is recommended.

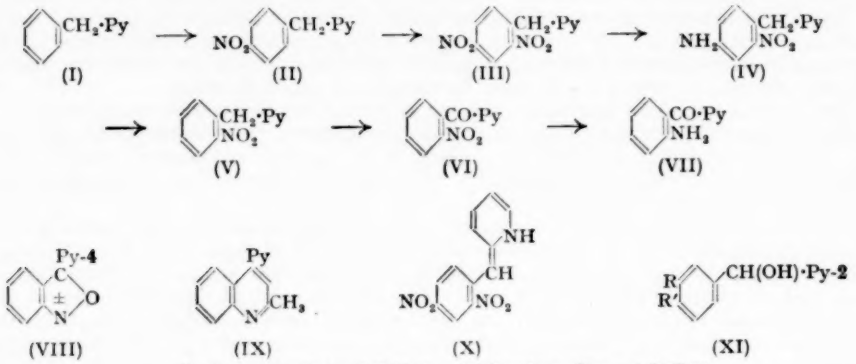
AMINO-KETONES of the types (VII) are required in these laboratories for a variety of experiments. Whilst we are examining other and, it is hoped, more flexible routes to such compounds, we have found it convenient so far to obtain (VII*a*) and (VII*b*) by the methods described below.

Conditions for effecting the series of reactions (I*a* ⟶ VII*a*), starting from 2-benzylpyridine, have recently been given by one of us (Schofield, *J.*, 1949, 2408). The present paper describes certain improvements in some of them, and the results obtained have served as models in extending the work to the analogous compounds (I*b* ⟶ VII*b*), originating in the relatively scarcer 4-benzylpyridine.

Tschitschibabin, Kuindshi, and Benewolenskaja (*Ber.*, 1925, **58**, 1580) nitrated 2-benzylpyridine in sulphuric acid, but Koenigs, Mensching, and Kirsch (*ibid.*, 1926, **59**, 1717), working with a mixture of 2- and 4-benzylpyridine, used fuming nitric acid. In a quantitative study, Bryans and Pyman (*J.*, 1929, 549) added 2-benzylpyridinium nitrate to sulphuric acid and isolated 58·8% of (II*a*). We have been able to isolate (II*a*) by the last method in 40% yield under preparative conditions, and so the adaptation by Schofield (*loc. cit.*) of Tschitschibabin's procedure is preferred.

The dinitro-compound (III*a*) was prepared by Tschitschibabin and his associates (*loc. cit.*) both by direct dinitration of 2-benzylpyridine and by further nitration of (II*a*), but these workers failed to record the essential experimental details. Clearly, successful direct dinitration would be attractive from the preparative point of view and we have

devised conditions which in small-scale experiments gave 41·4% of (III*a*) directly from 2-benzylpyridine, a yield slightly better than that (39%) previously obtained in two stages (Schofield, *loc. cit.*). However, this success could not be repeated on a large scale, and the two-stage process is still preferred.



"*a*" series: Py = 2-C_5H_4N. "*b*" series: Py = 4-C_5H_4N.

Wilson's original method (*J.*, 1931, 1936) for selectively reducing 2-(2 : 4-dinitrobenzyl)-pyridine to 2-(4-amino-2-nitrobenzyl)pyridine (IV*a*) was adapted by Schofield (*loc. cit.*) to give 75—80% yields in small-scale work, and rather less than this when large quantities were used. Slight modifications have now enabled us to prepare (IV*a*) quantitatively from (III*a*) on any desired scale.

The deamination of (IV*a*) to give 2-*o*-nitrobenzylpyridine (V*a*) was described by Wilson (*loc. cit.*) and later improved (Schofield, *loc. cit.*), to yield 48% of (V*a*). Both Wilson and Schofield used hypophosphorous acid prepared *in situ* from sodium hypophosphite and hydrochloric acid, the former purifying the product by vacuum-distillation. We have compared this with the direct use of commercial 30% hypophosphorous acid: the latter appears to be slightly preferable, but whilst increase in the amount used, from 15 to 30 equivalents, did give some improvement in yield, this was not sufficient to justify such a large expenditure of reagent. Kornblum, Cooper, and Taylor (*J. Amer. Chem. Soc.*, 1950, **72**, 3013), in recent experiments on the mechanism of hypophosphorous acid deaminations, found the rate of reaction to be increased by the addition to the reaction mixture of certain inorganic salts as catalysts, notably copper sulphate. It seemed to us possible that in the preparation of 2-*o*-nitrobenzylpyridine this might accelerate the deamination reaction compared with undesirable alternative decompositions of the diazonium compound; on the medium scale this device did in fact raise the yield of (V*a*) from 48% to 61·7%, but on the large-scale only 55·6% was obtained. In the light of this experience we would recommend the use of such catalysis in preparative deaminations utilising hypophosphorous acid, particularly when amines difficult of access are involved.

The yield obtained in the oxidation (V*a* ⟶ VI*a*) was unfortunately not accurately reported in the earlier paper (Schofield, *loc. cit.*), the 71% there claimed actually being the recovery of crude material. Of pure material there was obtained from this crude product only 55%. We now record a standardised oxidation procedure which consistently provides 57% of pure 2-*o*-nitrobenzoylpyridine.

Pure 4-*p*-nitrobenzylpyridine would appear to have been prepared only twice previously, Tschitschibabin and his co-workers (*loc. cit.*) obtaining it by means similar to those used in the 2-benzylpyridine series whereas Koenigs *et al.* (*loc. cit.*) obtained the compound only as an oil. In their quantitative studies Bryans and Pyman (*loc. cit.*) obtained 67·3% of (II*b*) from 4-benzylpyridine. The nitration method used by Schofield in preparing (II*a*) was not satisfactory in this case, but an adaptation of the procedure of Bryans and Pyman provided 53% of the desired product. The purity of the 4-benzylpyridinium nitrate, of which we describe the preparation, appeared to have little effect upon the reaction.

As in the 2-benzylpyridine series, Tschitschibabin *et al.* (*loc. cit.*) prepared the dinitro-compound (III*b*) both by direct dinitration of 4-benzylpyridine and by further nitration of (II*b*), but again details are lacking. Nitration of (II*b*) has now given 78·5% of the dinitro-compound (an overall yield of 41·6% from 4-benzylpyridine), whilst fuming nitric acid in sulphuric acid, used successfully by Huntress and Shaw (*J. Org. Chem.*, 1948, **13**, 674) in the case of 4-benzyl-2 : 6-dimethylpyridine, gave only 30·3% of the dinitro-compound.

4-(4-Amino-2-nitrobenzyl)pyridine, like its isomer, was isolated in almost quantitative yield through the agency of hydrogen sulphide and ammonia. In this series also, deamination of (IV*b*) was effected by means of hypophosphorous acid and copper sulphate, and the resulting 4-*o*-nitrobenzylpyridine (V*b*) was satisfactorily oxidised to 4-*o*-nitrobenzoylpyridine (VI*b*).

Unexpectedly, in view of the behaviour of the α-isomer, 4-*o*-nitrobenzoylpyridine was converted by an equivalent of stannous chloride into a mixture of the corresponding amine

FIG. 1. (I) 2-*Benzylpyridine* ; (II) 2-p-*Nitrobenzylpyridine* ; (III) 2-(2 : 4-*Dinitrobenzyl*)*pyridine* ; (IV) 2-(4-*Amino-2-nitrobenzyl*)*pyridine*. (*In absolute alcohol.*)

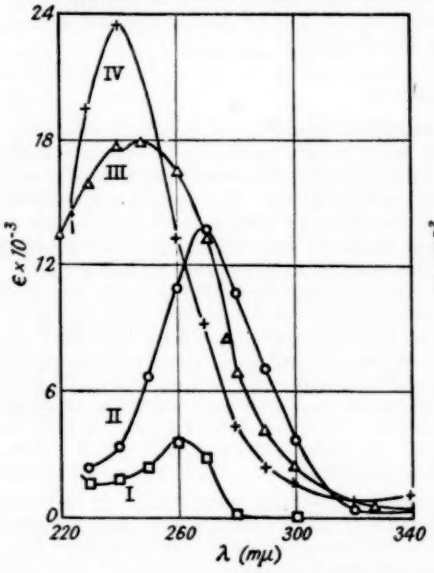
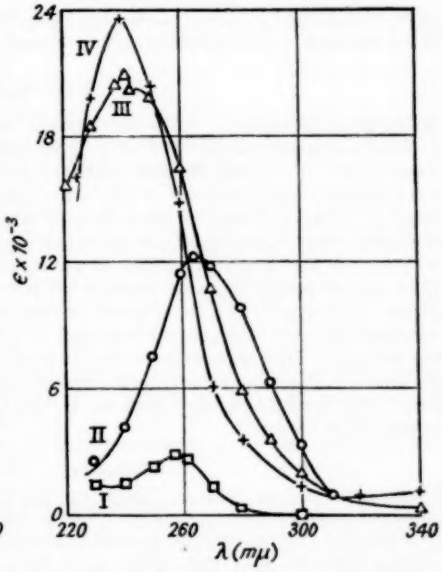


FIG. 2. (I) 4-*Benzylpyridine* ; (II) 4-p-*Nitrobenzylpyridine* ; (III) 4-(2 : 4-*Dinitrobenzyl*)*pyridine* ; (IV) 4-(4-*Amino-2-nitrobenzyl*)*pyridine*. (*In absolute alcohol.*)



(VII*b*) and the pyridylanthranil (VIII). Excess of the reducing agent gave solely the amine, and the anthranil could also be further reduced to this compound.

The orientation of the amino-ketone (VII*b*), and therefore of 4-*o*-nitrobenzoyl-, 4-*o*-nitrobenzyl-, and 4-(4-amino-2-nitrobenzyl)-pyridine, was proved by the preparation from it of 4-4′-pyridylquinaldine (IX*b*). 2-*o*-Aminobenzoylpyridine also reacted with acetone to give 4-2′-pyridylquinaldine. These derivatives of quinaldine have recently been described by Hey and Williams (*J.*, 1950, 1678).

Crystals of 2-(2 : 4-dinitrobenzyl)pyridine have the interesting property of changing to an intense violet colour when exposed to light, and of returning to yellow when kept in the dark. Neither the 4-isomer, nor any other member of the 2- and 4-series here described, exhibits this property. Tschitschibabin attributed the change to the conversion of (III*a*) by light into the structure (X), a conversion which is presumably rendered difficult in the 4-benzylpyridine derivative by the remoteness of the nitrogen atom in the pyridine ring. Both 2- and 4-(2 : 4-dinitrobenzyl)pyridine give yellow solutions in organic solvents, the colours of which are not obviously affected by light. We now record the ultra-violet absorption spectra of these and related compounds (Figs. 1 and 2), and it seems that in

solution they possess similar structures. It would be of interest to compare these spectra with those obtained by compounding the curves of suitable benzene and pyridine derivatives in order to detect any conjugation which may exist between the phenyl and pyridyl nuclei of benzylpyridine derivatives (cf. Braude, *J.*, 1949, 1902). We are collecting data for this purpose.

At the beginning of this work we envisaged the possibility of utilising Emmert and Asendorf's reaction (*Ber.*, 1939, **72**, 1188) to prepare carbinols of the type (XI) which it might have been feasible to oxidise and nitrate to give derivatives of (VI). This reaction has recently been exploited by Tilford, Shelton, and Van Campen (*J. Amer. Chem. Soc.*, 1948, **70**, 4001) for preparing a number of these carbinols. In the case of (XI; R = R′ = H) the American workers obtained a yield of 39%, whereas we could obtain no more than 22% of pure material. Again, with [XI; RR′ = CH_2O_2] Tilford *et al.* isolated an oil in 37% yield. However, Sperber, Papa, Schwenk, and Sherlock (*J. Amer. Chem. Soc.*, 1949, **71**, 887), who prepared the same compound by a different method, described it as a crystalline solid. In repeating the experiment of Tilford and his co-workers we were able to isolate 29% of product as an oil, but only 6% of the pure crystalline compound. These results, and others mentioned below, led us to abandon this route to the ketones (VI). (XI; RR′ = CH_2O_2) was oxidised to 2-(3 : 4-methylenedioxybenzoyl)-pyridine by means of aluminium *iso*propoxide and acetone.

Experimental

M. p.s are uncorrected. Ethereal extracts were dried with anhydrous sodium sulphate.

2- *and* 4-*Benzylpyridine*.—These compounds were readily prepared by Crook's method (*J. Amer. Chem. Soc.*, 1948, **70**, 416), modified in minor details, which we found to be superior in both convenience and efficiency to any other previously reported. The violent initial reaction between pyridine and benzyl chloride met with by previous workers and also in our own experiments using earlier methods does not occur under Crook's conditions. We found the same ratio of 2- and 4-benzylpyridine in the reaction mixture as is reported by this author.

2234 C.c. of benzyl chloride (used in 19 batches) thus provided 2315 g. of mixed benzylpyridines. Ether proved to be a more convenient solvent in extracting these compounds from the reaction mixture than the benzene–ligroin mixture used by Crook, which produced troublesome emulsions. The isomers were separated by fractional distillation under reduced pressure rather than at the near-atmospheric pressure used by Crook, and in this way the mixture provided 1632 g. of 2-benzylpyridine (b. p. 152—154°/20 mm.) and 503 g. of 4-benzylpyridine (b. p. 162—164°/20 mm.).

Derivatives of 2-benzylpyridine

2-*Benzylpyridinium Nitrate*.—Both of the following methods were used: (i) 2-Benzylpyridine (10 g.) and nitric acid (40 c.c.; 2N) saturated with sodium nitrate were shaken together at room temperature for ¼ hour, and the resulting white suspension was kept at 0° for 3 hours. The nitrate (14·6 g.), m. p. 109—116°, was collected and dried *in vacuo*.

(ii) (Cf. Huntress and Walter, *J. Amer. Chem. Soc.*, 1948, **70**, 3702.) A solution of 2-benzylpyridine (20 g.) in concentrated nitric acid (8·4 c.c.) and water (59 c.c.) was cooled in an ice–salt bath for 5 hours. The solid white mass was allowed to thaw at room temperature and the product was then collected and dried *in vacuo*. It (23·1 g.; m. p. 111—112°) was recrystallised from hot water (24 c.c.), giving small white crystals (19·9 g.), m. p. 107—110°. Basification of the combined aqueous filtrates, followed by ether-extraction, permitted the recovery of some 2-benzylpyridine (2·8 g.).

2-p-*Nitrobenzylpyridine*.—2-Benzylpyridinium nitrate (19·9 g.) was added during ½ hour to concentrated sulphuric acid (40 c.c.) cooled in ice. The mixture was warmed to 50° for 5 minutes and then poured on ice. Careful basification of the solution with ammonia, whilst cooling in a freezing mixture, gave a yellow solid which was dried on a porous plate *in vacuo*. 2-*p*-Nitrobenzylpyridine was thus obtained as a pale yellow solid (8·72 g.), m. p. 77—78° (40% based on the amount of 2-benzylpyridine used in preparing the nitrate).

2-(2 : 4-*Dinitrobenzyl*)*pyridine*.—Nitric acid (3 c.c.; *d* 1·5) was added dropwise, with shaking, to 2-benzylpyridine (5 g.) in concentrated sulphuric acid (22 c.c.) at −5° to 0°. The mixture was set aside for 2 hours at room temperature and then poured on ice, neutralised with aqueous ammonia, and extracted with ether (400 c.c.). Removal of the solvent gave tarry crystals

which after being twice crystallised from ethanol (charcoal) gave 2-(2 : 4-dinitrobenzyl)pyridine (3·2 g., 41·4%), m. p. 91—93°. On the 40-g. scale the yield fell to 25%.

2-(4-*Amino*-2-*nitrobenzyl*)*pyridine.*—A suspension of the above dinitro-compound (40 g.) in alcohol (200 c.c.) and aqueous ammonia (24 c.c.; *d* 0·88) was treated with hydrogen sulphide for 4 hours at 0° and for 2 hours whilst boiling under reflux. The resulting mixture was evaporated to dryness and the residue was extracted with dilute hydrochloric acid (700 c.c.). Gradual basification of the acid extract with aqueous ammonia, whilst cooling it in a freezing mixture, gave a light brown oil which quickly solidified. The resulting brown solid (34·6 g.), m. p. 106—112°, was satisfactory for use in the next stage. Omission of the initial saturation at 0° with hydrogen sulphide caused the reaction to fail.

2-o-*Nitrobenzylpyridine.*—(*a*) The amino-nitro-compound (10 g.) in hydrochloric acid (30 c.c.; 6N) was diazotised at 0° with aqueous sodium nitrite (10%), and the solution was treated with an ice-cold mixture of hypophosphorous acid (150 c.c. of 30%; 15 equivs.) and concentrated hydrochloric acid (50 c.c.). The solution was set aside at 0° for 24 hours and then basified with sodium hydroxide (5N) and extracted with ether. Concentration of the extract and distillation of the residue gave a yellow oil (4·5 g., 48%), b. p. 160—170°/0·4 mm.

The use of 30 equivs. of hypophosphorous acid raised the yield very slightly to 49·2%.

(*b*) To a solution of the diazonium salt prepared from the amine (10 g.) as above, were added at 0° hypophosphorous acid (150 c.c. of 30%), concentrated hydrochloric acid (50 c.c.), and powdered copper sulphate (0·5 g.). A vigorous evolution of nitrogen occurred for about 10 minutes. The solution was kept at 0° for 24 hours and then worked up as in (*a*), giving a yellow oil (5·8 g., 61·7%), b. p. 160—170°/0·5 mm. With 30 g. of the amine the yield fell to 55·6%.

2-o-*Nitrobenzoylpyridine.*—2-*o*-Nitrobenzylpyridine (4·1 g. of distilled material) and aqueous potassium permanganate (8 g. in 700 c.c. of water) were boiled under reflux, further amounts of permanganate (8 g. and 2 g.) being added 1½ hours and 2 hours from the time of starting. After refluxing for a total of 3 hours the mixture was decolorised with a few drops of alcohol, left to cool, and then filtered. The filter cake was digested with alcohol (300 c.c. in all), and the extract concentrated (charcoal), giving 2·5 g. of product, m. p. 117—118°. The use of undistilled 2-nitrobenzylpyridine gave much inferior yields, as did the conditions used by Huntress and Walter (*loc. cit.*) for oxidising 2-benzylpyridine, and also oxidation in aqueous acetone.

4-2′-*Pyridylquinaldine.*—2-*o*-Aminobenzoylpyridine (0·1 g.; Schofield, *loc. cit.*), alcohol (2 c.c.), acetone (2 c.c.), and 50% aqueous sodium hydroxide (1 c.c.) were refluxed together for 7 hours. After the resulting mixture had been diluted and the alcohol removed, the aqueous residue was acidified and extracted with ether. Basification of the aqueous layer and extraction with ether, followed by removal of the solvent, gave a yellow oil (0·12 g.) which provided colourless glistening prisms, m. p. 84—85° (Found: C, 81·7; H, 5·5. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5%), on crystallisation from ether–light petroleum (b. p. 40—60°). Hey and Williams (*loc. cit.*) give m. p. 84°.

Derivatives of 4-*benzylpyridine*

4-*Benzylpyridinium Nitrate.*—(i) A method similar to that described under (i) for the 2-isomer, except that the mixture was simply shaken at room temperature for 5 hours, gave 80—90% of a white crystalline product, m. p. 103—106° (the yield is estimated on the amount of 4-benzylpyridine recovered from the aqueous acid mixture).

(ii) A solution of 4-benzylpyridine (20 g.) in nitric acid (8·4 c.c.; *d* 1·42) and water (20 c.c.) was treated as in the preparation of the 2-isomer, and with allowance for recovered 4-benzylpyridine, gave an almost quantitative yield of the nitrate, m. p. 100—105°. 4-Benzylpyridinium nitrate is more soluble than its 2-isomer.

4-p-*Nitrobenzylpyridine.*—4-Benzylpyridinium nitrate (20 g.) was treated according to method (ii) for the preparation of 2-*p*-nitrobenzylpyridine. After dilution and basification of the reaction mixture the product was extracted with ether, and the extract concentrated to *ca.* 40 c.c. This solution was allowed to evaporate spontaneously to 15 c.c. and the product was collected (7·8 g.; m. p. 72—73°). Removal of the remaining ether from the filtrate gave an oil which slowly deposited more crystals of the required compound (*ca.* 2 g.; m. p. 72—73°). The total yield was 9·8 g. (53%). The method described by Schofield for the 2-isomer gave only about 15% of this compound.

4-(2 : 4-*Dinitrobenzyl*)*pyridine.*—(i) 4-*p*-Nitrobenzylpyridine (20 g.) was nitrated according to the method used by Schofield (*loc. cit.*) for its isomer. Basification with aqueous ammonia of the dilute reaction mixture, accompanied by ice-cooling, precipitated a grey oil which soon

solidified. It was extracted with ether (2·5 l.), and concentration of the extract provided yellow prisms (19·3 g.), m. p. 79—80°. Further concentration gave a minor crop (1·8 g.), m. p. 72—80°. A specimen of the compound recrystallised from ether formed large yellow prisms, m. p. 80—81° [Tschitschibabin *et al.* (*loc. cit.*) give m. p. 80—81°] (Found: C, 54·2; H, 3·6. Calc. for $C_{12}H_9O_4N_3$: C, 55·6; H, 3·5%). The picrate formed small yellow prisms, m. p. 152—153° (lit., 150—151°) (Found: C, 44·9; H, 2·4. Calc. for $C_{12}H_9O_4N_3,C_6H_3O_7N_3$: C, 44·3; H, 2·5%), after crystallisation from ethanol–ethyl acetate.

(ii) Fuming nitric acid (3 c.c.; *d* 1·5) was added dropwise to a solution of 4-benzylpyridine (5 g.) in concentrated sulphuric acid (34 c.c.) shaken at 0°. After remaining for 4 hours at room temperature the solution was poured on ice and neutralised with aqueous ammonia. The precipitated oil was extracted with ether (1 l.), and the extract concentrated. On seeding of the resultant brown oil and evaporation of the remaining ether, yellow prisms (2·3 g.) of the impure dinitro-compound, m. p. 74—76°, were obtained.

4-(4-*Amino*-2-*nitrobenzyl*)*pyridine*.—Reduction of the dinitro-compound (40 g.) as described above for its isomer gave a product (34·3 g.), m. p. 108—109°, suitable for use in the next stage. Pure 4-(4-*amino*-2-*nitrobenzyl*)*pyridine* separated from aqueous ethanol as mustard-yellow needles, m. p. 130—131° (Found: C, 63·1; H, 4·6. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8%).

4-o-*Nitrobenzylpyridine*.—The nitro-amine (10 g.) in hydrochloric acid (30 c.c.; 6N) was diazotised at 0° with aqueous sodium nitrite (10%). Ice-cold hypophosphorous acid (150 c.c. of 30%), concentrated hydrochloric acid (50 c.c.), and powdered copper sulphate (0·5 g.) were added, and the mixture was kept for 24 hours at 0°. Basification with sodium hydroxide solution and ether-extraction in the usual way provided a brown oil (6 g.) which on distillation gave 4-*o*-*nitrobenzylpyridine* (4·9 g.) as a pale yellow oil, b. p. 160—170°/0·4—0·6 mm. The *picrate*, prepared in alcohol, formed yellow plates (from methanol), m. p. 156—157° (Found: C, 49·1; H, 3·0. $C_{12}H_{10}O_2N_2,C_6H_3O_7N_3$ requires C, 48·8; H, 3·0%).

4-o-*Nitrobenzoylpyridine*.—Obtained in 40% yield by the procedure described above for its isomer, 4-o-*nitrobenzoylpyridine* crystallised from hot water as long thin white needles, m. p. 77—78° (Found: C, 62·2; H, 3·6. $C_{12}H_8O_3N_2$ requires C, 63·1; H, 3·5%).

Reduction of 4-o-*Nitrobenzoylpyridine*.—(i) The nitro-compound (5 g.) in concentrated hydrochloric acid (5 c.c.) was treated with stannous chloride (15 g.) in the same solvent (20 c.c.) and after being heated for 1 hour at 95° the mixture was set aside for 5 hours at room temperature. Basification and ether-extraction, followed by removal of the solvent, gave a yellow solid (3·3 g.), m. p. (80) 92—95°. This crude product was diazotisable, as shown by the usual tests, but several crystallisations from aqueous methanol gave a compound which was not an amine. Pure 3-4′-*pyridylanthranil* formed fawn-coloured needles, m. p. 124—125° (Found: C, 73·1; H, 4·2; N, 14·3. $C_{12}H_8ON_2$ requires C, 73·45; H, 4·1; N, 14·3%), from dilute methanol. Reduction of this compound by excess of stannous chloride gave the amine described in (ii).

(ii) 4-*o*-Nitrobenzoylpyridine (1·5 g.) in concentrated hydrochloric acid (7·5 c.c.) was treated with stannous chloride (18 g.) in the same solvent (23 c.c.), and the mixture was heated at 95° for 1 hour and then kept for 5 hours at room temperature. After working up in the usual way, 4-o-*aminobenzoylpyridine* (1·3 g.) was obtained. It crystallised from aqueous methanol as yellow leaflets, m. p. 160—161° (Found: C, 72·7; H, 4·8; N, 14·2. $C_{12}H_{10}ON_2$ requires C, 72·7; H, 5·1; N, 14·1%).

4-4′-*Pyridylquinaldine*.—Prepared in the manner described above for the 2′-isomer this compound crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 103—104°, alone or mixed with a specimen (m. p. 103—104°) prepared by the method of Hey and Williams (*loc. cit.*) (Found: C, 81·6; H, 5·6%).

Emmert–Asendorf Reactions.—Methods " A " and " B " of Tilford, Shelton, and Van Campen (*loc. cit.*) were employed. Ether was used instead of toluene for all extractions. Phenyl-2-pyridylcarbinol was obtained in 22% yield by method " A ". Experiments with *m*-chlorobenzaldehyde using both methods gave no homogeneous product. 3 : 4-Methylenedioxyphenyl-2-pyridylcarbinol was prepared by method " B " in 29% yield. This oil crystallised to give feathery needles of the pure carbinol (6%), m. p. 142—143°. Sperber *et al.* (*loc. cit.*) give m. p. 142—142·5°. The *picrate* separated from ethanol as yellow needles, m. p. 178—180° (Found: C, 49·9; H, 3·0. $C_{13}H_{11}O_3N,C_6H_3O_7N_3$ requires C, 49·8; H, 3·0%).

2-(3 : 4-*Methylenedioxybenzoyl*)*pyridine*.—The above carbinol (2 g.) was refluxed for 16 hours with aluminium *iso*propoxide (5·6 g.), dry benzene (35 c.c.), and dry acetone (70 c.c.). After removal of most of the solvents the residue was extracted with dilute sulphuric acid, and the acid solution was then basified and extracted with ether. On removal of the ether and dissolution of the residue in alcohol (10 c.c.), 0·27 g. of starting material was recovered. Treatment of the

alcohol solution with picric acid and recrystallisation of the product from ethanol gave yellow needles (1·08 g.) of the ketone *picrate*, m. p. 153—154° (Found: C, 49·5; H, 3·0. $C_{13}H_9O_3N,C_6H_3O_7N_3$ requires C, 50·0; H, 2·65%).

The authors express their indebtedness to the Chemical Society, to the University College of the South West, and to Imperial Chemical Industries Limited for financial assistance, and also to Professor D. H. Hey who kindly provided a specimen of 4-4′-pyridylquinaldine.

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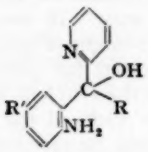
105. *Some o-Aminophenyl-pyridyl- and -quinolyl-carbinols.*

By A. J. NUNN and K. SCHOFIELD.

The reactions of 2-pyridyl- and 3-pyridyl-lithium with *o*-aminoacetophenone and related compounds to give 2-aminophenyl-pyridylcarbinols are described. 4-*o*-Aminobenzoylpyridine reacts normally with Grignard reagents. A further study of the reaction between 2-amino-4′-methoxybenzophenone and 2-pyridylmethyl-lithium (Schofield, *J.*, 1949, 2408) has been made, and reactions between the latter, and also 2-quinolylmethyl-lithium, and other 2-aminobenzophenones have been carried out.

CARBINOLS of the types (I—V) were required for synthetic work in the cinnoline series. Preliminary experiments on the preparation of a few such compounds have already been described (Schofield, *J.*, 1949, 2408). Thus 1-*o*-aminophenyl-1-2′-pyridylethanol (I; R = Me, R′ = H) and 1-*o*-aminophenyl-2-phenyl-1-2′-pyridylethanol (I; R = Ph·CH_2, R′ = H) were obtained by treating 2-*o*-aminobenzoylpyridine (VI) with the appropriate Grignard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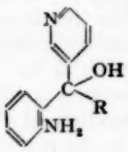
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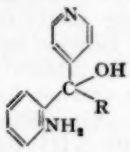
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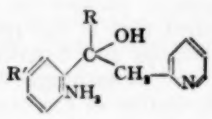
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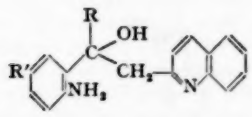
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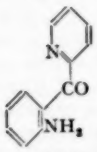
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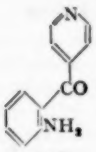

(VII)

reagents. The carbinols (IV; R′ = H, R = Ph, or MeO·C_6H_4) and (V; R = H, R = Ph, and MeO·C_6H_4) were prepared from 2-aminobenzophenone or 2-amino-4′-methoxybenzophenone by the action of 2-pyridylmethyl- or 2-quinolylmethyl-lithium.

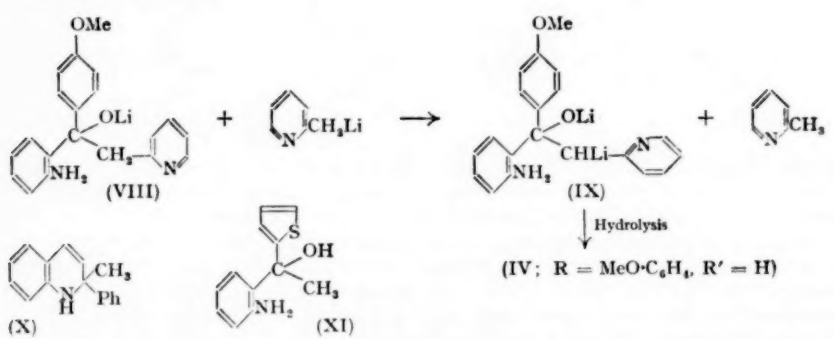
This paper describes a more convenient route to compounds of the type (I) and its application to the preparation of carbinols (II). Further, a synthesis of compounds represented by (III) is given. Also, the preparation of the carbinols (IV) and (V) mentioned above has been re-examined, and new examples have been obtained.

Whilst the ketone (VI) reacts satisfactorily with Grignard reagents it is so inaccessible (see the preceding paper) as to make an alternative and more flexible method of synthesising the carbinols (I) essential if they are to be available in any number. A range of substituted *o*-aminoacetophenones and *o*-aminopropiophenones is now readily obtainable (Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646; Keneford and Simpson, *J.*, 1948, 354; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405) and we have found it convenient to treat these with the little used 2-pyridyl-lithium. The formation of this

reagent in 62% yield, by halogen–metal exchange between 2-bromopyridine and *n*-butyl-lithium, has been described by Spatz (*Iowa State Coll. J. Sci.*, 1942—1943, **17**, 129) according to whom the chief difficulty arises from the tendency of *n*-butyl-lithium to add to the azomethine linkage of the pyridine derivative, but under suitable conditions this is rendered negligible, as shown by Adamson and Billinghurst (*J.*, 1950, 1039). The latter authors treated certain alkyl ketones with four equivalents of 2-pyridyl-lithium and obtained carbinols in good yield. Using, for economy, two equivalents of 2-pyridyl-lithium we have prepared (I; R = Me, R′ = H) in 42% yield from *o*-aminoacetophenone. In similar processes the appropriate ketones gave (I; R = Me, R′ = Cl) and (I; R = Et; R′ = H). Likewise, 3-pyridyl-lithium (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1940, **62**, 446) reacted with *o*-aminoacetophenone and *o*-aminopropiophenone to form (II; R = Me) and (II; R = Et) respectively.

Unfortunately 4-pyridyl derivatives would appear not to be accessible by similar methods. 4-Pyridyl-lithium seems not to have been prepared and would probably be highly susceptible to addition to the pyridine–azomethine linkage. In the same way, attempts to prepare 4-pyridylmethyl-lithium gave addition products (cf. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 571). For this reason we have used 4-*o*-amino-benzoylpyridine (VII) (Nunn and Schofield, preceding paper) as a source of carbinols of type (III). The ketone reacted readily with methyl- and ethyl-magnesium iodides, giving (III; R = Me and Et).

We extended our earlier incomplete work (Schofield, *loc. cit.*) on the reaction of 2-aminobenzophenone and 2-amino-4′-methoxybenzophenone with 2-pyridylmethyl- and 2-quinolylmethyl-lithium. By use of about one equivalent each of the lithium reagent and the ketone there were obtained originally 30% of (IV; R = Ph, R′ = H), 23% of (V; R = Ph, R′ = H), 26% of (IV; R = MeO·C_6H_4, R′ = H; owing to an error in transcription the yield appeared in print as 49%), and 35% of (V; R = MeO·C_6H_4, R′ = H). In the present work (IV; R = MeO·C_6H_4, R′ = H) was chosen for the chief examination, because its sparing solubility makes its isolation easy. It was first established that in the reaction between equivalent quantities of 2-amino-4′-methoxy-benzophenone and 2-pyridylmethyl-lithium the material not accounted for previously was present as unchanged ketone, and not, as had seemed possible, as the ethylene formed by dehydration of the carbinol. A possible explanation of the low yield of the latter seemed to be that the intermediate (VIII) formed in the reaction might be capable itself of consuming 2-pyridylmethyl-lithium [to give (IX)], and so of preventing that reagent from attacking the ketone :



We therefore examined the method of " alternate additions " (Weiss and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 2023; P. M. Foreman, Thesis, Univ. Stanford, 1943, " The Acylation and Aroylation of α- and γ-Alkylquinolines "). The procedure is exemplified in the Experimental section, but unfortunately the results were inexplicably erratic and no unambiguous improvement can be claimed.

We subsequently noticed that the use of two and three equivalents of 2-pyridylmethyl-

lithium with 2-amino-4′-methoxybenzophenone raised the recovery of the carbinol to 51% and 78% respectively. The use of two equivalents of the reagent similarly improved the efficiency of the reaction with 2-aminobenzophenone. Therefore, as a compromise between efficiency and economy, we used two equivalents of the lithium reagent to one of the ketone in all subsequent experiments. 2-Amino-4′-methyl- and 2-amino-5-chlorobenzophenone thus provided 1-*o*-aminophenyl-2-2′-pyridyl-1-*p*-tolyl- (IV; R = Me·C_6H_4, R′ = H) and 1-(2-amino-5-chlorophenyl)-1-phenyl-2-2′-pyridyl-ethanol (IV; R = Ph, R′ = Cl).

The use of excess of the lithium reagent also led to increased recovery of (V; R = Ph, R′ = H) and (V; R = MeO·C_6H_4, R′ = H), and we now describe the further examples, 1-*o*-aminophenyl-2-2′-quinolyl-1-*p*-tolyl- (V; R = Me·C_6H_4, R′ = H) and 1-(2-amino-5-chlorophenyl)-1-phenyl-2-2′-quinolyl-ethanol (V; R = Ph, R′ = Cl). The lower yields obtained in the preparation of the quinolyl-, as compared with the pyridyl-carbinols, may be due to the tendency for addition reactions to occur at the quinaldine–azomethine linkage. Thus, Leonard and Boyer (*J. Amer. Chem. Soc.*, 1950, **72**, 2980) sought to prepare quinolylacetic acid by carboxylation of 2-quinolylmethyl-lithium, but obtained mainly (X), the product of addition of phenyl-lithium to quinaldine.

The carbinols (IV and V; R = Me, R′ = H) would be of special interest to us. Low yields of impure compounds resulted from reactions between equivalent quantities of *o*-aminoacetophenone and 2-pyridylmethyl- and 2-quinolylmethyl-lithium. Using excess of the former reagent we have, however, isolated mediocre yields of (IV; R = Me, R′ = H), but have not yet been successful in the quinoline series.

2-Thienyl-lithium reacted readily with *o*-aminoacetophenone to give 1-*o*-aminophenyl-1-2′-thienylethanol (XI).

Experiments with the carbinols mentioned above will be described later.

Experimental

M. p.s are uncorrected. All lithium reagents were prepared under an atmosphere of nitrogen. The ether and benzene used were dried over sodium. All ethereal extracts were dried over anhydrous sodium sulphate.

Reactions with 2- and 3-Pyridyl-lithium.

1-o-*Aminophenyl*-1-2′-*pyridylethanol.*—*n*-Butyl bromide (14·35 g.) in dry ether (40 c.c.) was added dropwise during ½ hour to lithium wire (1·80 g.) in dry ether (80 c.c.) at −20° to −15°, with stirring. The mixture was stirred for 1 hour at 0—10° and then filtered through glass wool. The solution was cooled to −60°, and then 2-bromopyridine (14·96 g.) in ether (30 c.c.) was added during 15 minutes and the whole was stirred for 5 minutes more. *o*-Aminoacetophenone (6·43 g.) in ether (50 c.c.) was added during 20 minutes, after which the temperature was allowed to rise to −15° and the stirring continued for 1 hour. The yellow complex was decomposed with water (50 c.c.), and the mixture shaken with aqueous ammonia and extracted with ether. Concentration of the extract gave yellow needles of the carbinol (3·70 g.), m. p. 95—96°, and subsequently a second crop (0·60 g.), m. p. 92—93°, was obtained.

If after decomposition with water the reaction mixture was extracted with ether, without being washed with ammonia, removal of the ether provided a viscous brown oil. Dissolution of this in methanol, followed by addition of ether, gave yellow crystals. Several crystallisations from methanol–ether gave yellow prisms of 1-o-*aminophenyl*-1-2′-*pyridylethanol hydrobromide*, m. p. 172—173° (Found: C, 52·9; H, 4·2; N, 8·7. $C_{13}H_{15}ON_2Br$ requires C, 52·9; H, 5·1; N, 9·5%).

1-(2-*Amino*-5-*chlorophenyl*)-1-2′-*pyridylethanol.*—5-Chloro-2-aminoacetophenone (8·1 g.) in ether (50 c.c.) was added during 20 minutes to 2-pyridyl-lithium (from 14·96 g. of 2-bromopyridine) at −60°. After being stirred for 1 hour at −15° the complex was decomposed with water, and the mixture was shaken with aqueous ammonia and extracted with ether. Concentration of the extract gave the *carbinol* (6·35 g.), m. p. 108—113°. It crystallised from ethanol as pale yellow needles (5·4 g.), m. p. 115—116° (Found: C, 62·9; H, 5·3. $C_{13}H_{13}ON_2Cl$ requires C, 62·8; H, 5·3%). In one experiment, despite the treatment with ammonia, the carbinol separated as its hydrobromide and the free base was liberated by grinding this with aqueous ammonia (*d* 0·88).

1-o-*Aminophenyl*-1-2′-*pyridylpropanol*.—By the method described for 1-*o*-aminophenyl-1-2′-pyridylethanol, *o*-aminopropiophenone (7·2 g.) gave the corresponding carbinol (5·7 g.) as yellow prisms, m. p. 82—84°. 1-o-*Aminophenyl*-1-2′-*pyridylpropanol* formed colourless prisms, m. p. 83—84°, from ether (Found : C, 73·4; H, 7·05. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·1%).

1-o-*Aminophenyl*-1-3′-*pyridylethanol*.—The same method was employed as for the 2-pyridyl-compound. 3-Pyridyl-lithium when treated with *o*-aminoacetophenone (6·43 g.) yielded yellow prisms of the product (3·60 g.), m. p. 143—145°, together with a second crop (0·65 g.), m. p. 134—142°. The pure *carbinol* (3·55 g.) separated from benzene as yellow prisms, m. p. 147—148° (Found : C, 73·9; H, 6·5. $C_{13}H_{14}ON_2$ requires C, 72·8; H, 6·6%).

1-o-*Aminophenyl*-1-3′-*pyridylpropanol*.—3-Pyridyl-lithium was treated with *o*-aminopropiophenone (7·2 g.) in the usual way. Decomposition of the reaction mixture with water gave a yellow precipitate (6·3 g.), m. p. 179—180°, which was collected and dried. 1-o-*Aminophenyl*-1-3′-*pyridylpropanol* crystallised from aqueous methanol in clusters of light brown needles, m. p. 185—186° (Found : C, 73·0; H, 7·5%).

1-o-*Aminophenyl*-1-4′-*pyridylethanol*.—4-*o*-Aminobenzoylpyridine (0·82 g.) in ether (100 c.c.) was added in one portion to a stirred Grignard reagent [from magnesium (0·46 g.), methyl iodide (2·75 g.), and ether (34 c.c.)] and the resulting red suspension was heated and stirred under reflux for 1½ hours. Decomposition with ice and ammonium chloride, followed by ether-extraction, provided the substantially pure product (0·62 g.). The *carbinol* crystallised from ether as colourless needles, m. p. 199—200° (Found : C, 72·4; H, 6·6%).

1-o-*Aminophenyl*-1-4′-*pyridylpropanol*.—Prepared by the above method, with ethylmagnesium iodide, this *compound* formed fawn-coloured needles (from alcohol), m. p. 181—182° (Found : C, 73·2; H, 6·4; N, 12·2%).

Reactions with 2-Pyridyl- and 2-Quinolyl-methyl-lithium.

The efficiency of the procedure used in preparing these reagents was occasionally checked by titration of the intermediate phenyl-lithium (*J. Amer. Chem. Soc.*, 1932, **54**, 1957), which was formed in yields varying only slightly from 87·5%.

o-*Aminophenyl*-p-*methoxyphenyl*-2-*pyridylmethylcarbinol*.—(i) Bromobenzene (18·01 g.) in ether (40 c.c.) was added during ½ hour to lithium (1·58 g.) with stirring, and the mixture was then refluxed gently with continued stirring for ¾ hour. 2-Picoline (9·53 g.) was added, and the dark red mixture stirred for 1 hour at room temperature. The ketone (23·28 g.) in benzene (50 c.c.) and ether (50 c.c.) was then added during ¼ hour, and the orange suspension was stirred for 4 hours at room temperature and 1 hour under reflux. After cooling, it was decomposed with water (150 c.c.) and set aside for 12 hours. The crystalline product was collected (8·25 g.; m. p. 148—149°), washed with a little ether, and dried. Recrystallisation from methanol gave soft cream-coloured needles, m. p. 153—154°. Variable amounts of the original ketone could be recovered from the ether–benzene layer by concentration and long storage.

(ii) In a similar procedure, except that the 1 hour of refluxing was omitted, the ketone (14·73 g.) in benzene (50 c.c.) reacted with 2-pyridylmethyl-lithium (2 equivs.; from 2·00 g. of lithium in 100 c.c. of ether) to give a crude product (13·1 g.; m. p. 143—145°) which provided 10·7 g. (51·5%) of pure material, m. p. 151—152°, after crystallisation. Small amounts of crude product could be obtained by concentration of the reaction solution.

Under the same conditions the use of 3 equivalents of the reagent gave 78% of product.

(iii) Solutions of 2-amino-4′-methoxybenzophenone (22·84 g.) in benzene (80 c.c.) and of phenyl-lithium (from 1·55 g. of lithium) in ether were prepared. To a preparation of 2-pyridylmethyl-lithium (from 1·55 g. of lithium) in ether was added one-half of the ketone solution (causing the red solution to become yellow-brown), and after ¼ hour one-half of the phenyl-lithium solution (which restored the original red colour). Subsequently, ketone and phenyl-lithium were added alternately, in the amounts, after the times, and with the effect listed : ¼, ½ hour, yellow red; ¼, 1 hour, red; ⅛, ½ hour, yellow red; ⅛, ½ hour, purple red; $\frac{1}{16}$, ¼ hour, orange red; $\frac{1}{16}$, ¼ hour, purple red; $\frac{1}{32}$, ¼ hour, orange red; $\frac{1}{32}$, ¼ hour, purple red; remainder of the ketone, ¼ hour, orange red. After 2½ hours' stirring at room temperature, and working up in the usual way, the mixture gave 16·0 g. of the carbinol, m. p. 149—150°.

Similar yields were obtained in three successive experiments, but subsequent runs failed.

1-o-*Aminophenyl*-1-*phenyl*-2-2′-*pyridylethanol*.—2-Aminobenzophenone (10·6 g.) in benzene (50 c.c.) was added to 2-pyridylmethyl-lithium (2 equivs.; from 1·64 g. of lithium in 100 c.c. of ether) during 10 minutes, and the mixture was then stirred for 4 hours at room temperature. Worked up as usual the reaction gave a crude product (10·65 g.; m. p. 140—142°) which was

crystallised from ethanol, needles of the carbinol (9·3 g., 59·6%), m. p. 161—162°, being obtained. The ether–benzene layer was concentrated to a small volume and benzene was then added; after some days, more (0·88 g.) of the crude carbinol, m. p. 146—150°, separated.

1-o-*Aminophenyl*-2-2′-*pyridyl*-1-p-*tolylethanol*.—2-Amino-4′-methylbenzophenone (6·36 g.; Kippenberg, *Ber.*, 1897, **30**, 1133) in benzene (30 c.c.) was added to 2-pyridylmethyl-lithium (2 equivs.; from 0·93 g. of lithium) in ether (100 c.c.), and the orange-red suspension was then stirred for 4 hours. Concentration of the ether–benzene solution, obtained after decomposition in the usual way, at 95° and under vacuum gave a red glass which after dissolution in ethanol (20 c.c.) provided a crystallne solid (5·57 g.), m. p. 112—113°. The *carbinol* separated from aqueous ethanol as cream-coloured needles, m. p. 115—116° (Found: C, 79·7; H, 6·6. $C_{20}H_{20}ON_2$ requires C, 78·9; H, 6·6%).

1-(2-*Amino*-5-*chlorophenyl*)-1-*phenyl*-2-2′-*pyridylethanol*.—By the method just described 2-amino-5-chlorobenzophenone (7·13 g.; Angel, *J.*, 1912, **101**, 516) gave a yellow brown product (4·51 g.), m. p. 139—143°. The *carbinol* crystallised from ethanol in yellow prisms (3·77 g.), m. p. 143—144° (Found: C, 69·9; H, 5·4. $C_{19}H_{17}ON_2Cl$ requires C, 70·3; H, 5·3%).

1-o-*Aminophenyl*-1-*phenyl*-2-2′-*quinolylethanol*.—This compound was prepared by the method described more fully below for its methoxyphenyl analogue. 2-Aminobenzophenone (12·0 g.) with 2 equivalents of 2-quinolylmethyl-lithium gave a product (15·8 g.), m. p. 130—131°. White needles of the carbinol (7·8 g., 38·3%), m. p. 158—159°, were obtained from methanol.

1-o-*Aminophenyl*-1-p-*methoxyphenyl*-2-2′-*quinolylethanol*.—(i) 2-Amino-4′-methoxybenzophenone (18·56 g.) in benzene (50 c.c.) was added to 2-quinolylmethyl-lithium (1 equiv.; from 1·26 g. of lithium in 100 c.c. of ether) during ¼ hour. After 5 hours' stirring at room temperature the red solution was decomposed with water (100 c.c.), and the carbinol (13·18 g.), m. p. 147—148°, was collected. White feathery crystals (9·3 g., 30·9%), m. p. 154—155°, were obtained by digestion with ethanol (700 c.c.).

(ii) With 2 equivalents of the lithium reagent (from 1·45 g. of lithium in 100 c.c. of ether) the ketone (10·68 g.) gave by the same method 48·1% of purified product.

1-(2-*Amino*-5-*chlorophenyl*)-1-*phenyl*-2-2′-*quinolylethanol*.—2-Amino-5-chlorobenzophenone (6·75 g.) in benzene (30 c.c.) was added during 10 minutes to 2-quinolylmethyl-lithium (from 0·90 g. of lithium in 100 c.c. of ether). The mixture was stirred for 4 hours and decomposed with water (100 c.c.). The ether–benzene layer was concentrated to a small volume (15 c.c.), alcohol (10 c.c.) was added, and the yellow crystals (5·83 g.), m. p. 130—143°, which separated on cooling, were collected. Pale yellow needles of the *carbinol* (3·60 g.), m. p. 154—155°, were obtained from ethanol (Found: C, 73·4; H, 5·4. $C_{23}H_{19}ON_2Cl$ requires C, 73·7; H, 5·1%).

1-o-*Aminophenyl*-2-2′-*quinolyl*-1-p-*tolylethanol*.—2-Amino-4′-methylbenzophenone (5·26 g.) in benzene (30 c.c.) was added to 2-quinolylmethyl-lithium (from 0·77 g. of lithium in 100 c.c. of ether), and the mixture was stirred for 4 hours. After the addition of water (100 c.c.) the grey precipitate was collected (3·95 g.; m. p. 125—127°). Yellow needles of the *carbinol*, m. p. 137—138°, separated from alcohol (Found: C, 81·6; H, 6·55. $C_{24}H_{22}ON_2$ requires C, 81·3; H, 6·3%).

1-o-*Aminophenyl*-3-2′-*pyridylpropan*-2-*ol*.—*o*-Aminoacetophenone (4·73 g.) in benzene (30 c.c.) was added during 10 minutes to 2-pyridylmethyl-lithium (2 equivs.; from 1·08 g. of lithium in 80 c.c. of ether). The mixture was stirred for 1 hour and decomposed with water (100 c.c.). Extraction with ether and removal of this solvent gave a viscous red oil (7·46 g.) which was distilled at 0·4—0·5 mm. The fraction, b. p. 154—184° (4·23 g.), was crystallised from ether–light petroleum (b. p. 60—80°), giving pale yellow needles (2·10 g.; m. p. 67—70°). Two further crystallisations from the same solvent mixture gave colourless prisms of the *carbinol*, m. p. 84—85° (Found: C, 73·6; H, 7·3. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·1%).

1-o-*Aminophenyl*-1-2′-*thienylethanol*.—Redistilled thiophen (8·86 g.) in ether (10 c.c.) was added to phenyl-lithium (from 1·5 g. of lithium in 100 c.c. of ether), and the mixture was refluxed for 2 hours. *o*-Aminoacetophenone (7·18 g.) in ether (50 c.c.) was added dropwise during ¼ hour at −15° and the brown solution was then stirred for 1 hour at room temperature. After decomposition of the complex with water (50 c.c.) the mixture was extracted with ether. This ethereal extract was washed with water and shaken with hydrochloric acid (600 c.c. of 15%), and the acid solution was then washed with a small amount of ether. Basification of the acid layer with aqueous ammonia followed by ether-extraction provided a dark brown oil (9·15 g.) which was distilled at 1·0—1·5 mm. The oil provided several fractions boiling over a very wide range, but those collected (5·32 g. in all) from 142° to 182° slowly crystallised. They were combined and recrystallised from ether–light petroleum (b. p. 60—80°), giving a pale yellow

product (3·67 g.), m. p. 62—64°. The pure *carbinol* formed colourless prisms, m. p. 66—67°, from the same solvent mixture (Found: C, 65·4; H, 6·3. $C_{13}H_{13}ONS$ requires C, 65·7; H, 6·0%).

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WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER. [*Received, October 3rd,* 1951.]

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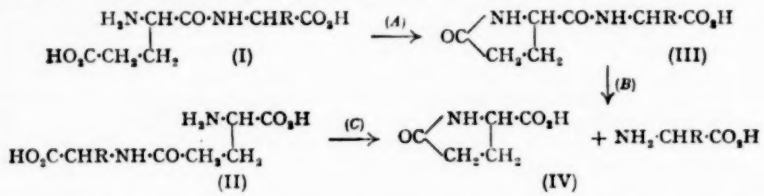
106. *Amino-acids and Peptides. Part VII.* The Autohydrolysis of Glutamyl-peptides.*

By W. J. LE QUESNE and G. T. YOUNG

It was suggested in Part II (*J.*, 1950, 1959) that the autohydrolysis of α-glutamyl-peptides proceeds through the pyrrolidone derivative (equations *A* and *B*) whilst γ-glutamyl-peptides undergo an intramolecular substitution (equation *C*) resulting in fission of the peptide bond. Further evidence in support of these mechanisms is now presented.

IN Part II (*J.*, 1950, 1959) a brief report was made of experiments in which aqueous solutions of α- (*e.g.*, I) and γ-L-glutamyl-peptides (*e.g.*, II) were allowed to undergo hydrolysis at 100°. Partition chromatography of the products after 24 hours showed the presence of appreciable amounts of glutamic acid in two cases only, those of α- and γ-L-glutamyl-L-glutamic acids. Hydrolysis with 0·5N-acid gave the expected products including glutamic acid in all cases, whilst a control experiment showed that under similar conditions a solution of glutamic acid still gave a strong colour with ninhydrin. We suggested that autohydrolysis of α- and γ-glutamyl-peptides is preceded or accompanied (respectively) by cyclisation to pyrrolidone derivatives, which do not react with ninhydrin, and we now offer further evidence consistent with these mechanisms.



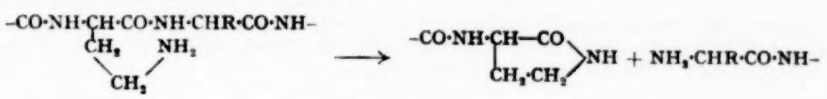
Investigating first the case of α-glutamyl-peptides, we examined the products of autohydrolysis by means of paper partition chromatography in butanol, spraying the chromatogram with methyl-orange solution to detect 5-ketopyrrolidine-2-carboxylic acid (IV) and the intermediate 5-ketopyrrolidine-2-carboxyamido-acids (III). After 24 hours' heating at 100°, α-L-glutamyl-L-aspartic acid gave a chromatogram indicating the presence of the acid (IV), which was also isolated in small yield together with aspartic acid. From α-L-glutamylglycine both the acid (IV) and *N*-(5-ketopyrrolidine-2-carbonyl)glycine (III; R = H) were identified chromatographically, the hydrolysis stage being incomplete. From α-L-glutamyl-L-glutamic acid, *N*-(5-keto-L-pyrrolidine-2-carbonyl)-L-glutamic acid was isolated and identified with an authentic sample. The R_F value of this material in butanol is too close to that of 5-ketopyrrolidine-2-carboxylic acid to enable the latter to be distinguished with certainty, but a small amount of glutamic acid was isolated from the products and some hydrolysis had undoubtedly occurred. α-L-Glutamyl-L-tyrosine gave *N*-(5-keto-L-pyrrolidine-2-carbonyl)-L-tyrosine, identified on the chromatogram by comparison with a synthetic sample, but no 5-ketopyrrolidine-2-carboxylic acid. This agrees with the earlier observation that no tyrosine is formed, and here cyclisation appears to

* Part VI, *J.*, 1952, 24.

have occurred but not hydrolysis. α-L-Glutamyl-L-valine behaved similarly, in that neither the acid (IV) nor valine was found after 24 hours; the presence of *N*-(5-keto-L-pyrrolidine-2-carbonyl)-L-valine was inferred from the chromatogram, but in the absence of an authentic sample we were unable to confirm its identity.

The behaviour of synthetic samples of *N*-(5-keto-L-pyrrolidine-2-carbonyl)-glycine and -L-glutamic acid is consistent with the above interpretation; after 24 hours in water at 100°, the former gave the acid (IV) and glycine besides some unchanged material, whilst the latter appeared to be mainly unchanged. A crude sample of 5-keto-L-pyrrolidine-2-carbonyl-L-tyrosine gave no 5-ketopyrrolidine-2-carboxylic acid under these conditions. After similar heating of an aqueous solution of 5-ketopyrrolidine-2-carboxylic acid, both glutamic acid and unchanged material were detected chromatographically.

Partition chromatography of the products obtained on heating γ-L-glutamyl-glycine, -L-glutamic acid, and -L-aspartic acid for 24 hours at 100° showed the presence of the acid (IV) in each case, identity being confirmed by isolation in the first two experiments. From the second-named peptide glutamic acid also was isolated; this again suggests that the ring compound is a primary product of the hydrolysis and is not formed subsequently from glutamic acid. This is consistent with earlier observations that glutathione (Hopkins, *J. Biol. Chem.*, 1929, **84**, 314) and glutamine (Vickery, Pucher, Clark, Chibnall, and Westall, *Biochem. J.*, 1935, **29**, 2710) give 5-ketopyrrolidine-2-carboxylic acid when heated in aqueous solution. If mechanism (*C*) is correct, then hydrolysis under these conditions is in fact an intramolecular substitution, and the lability of γ-glutamyl-amide and -peptide bonds is due to the presence of the free α-amino-group in a position suitable for stable ring formation. This interpretation agrees with the known stability of the amide group in peptides such as L-leucyl-L-glutamine (Chibnall and Westall, *Biochem. J.*, 1932, **26**, 122; Melville, *ibid.*, 1935, **29**, 179) and of asparagine. It is tempting to suggest that under suitable conditions αγ-diaminobutyric acid may in analogous fashion form a source of instability in peptide chains:



Experimental

All m. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss.

N-(5-*Keto*-L-*pyrrolidine*-2-*carbonyl*)-L-*glutamic Acid*.—Diethyl 5-keto-L-pyrrolidine-2-carbonyl-L-glutamate (0·3 g.; Angier *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 74) in N-sodium hydroxide (2 ml.) was set aside for 2 hours. N-Hydrochloric acid (2 ml.) was added and the solution evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol and the solution evaporated *in vacuo*; the remaining oil crystallised under ethyl acetate. The *N*-(5-*keto*-L-*pyrrolidine*-2-*carbonyl*)-L-*glutamic acid* (0·19 g., 77%) had m. p. 176—178°. A portion, recystallised from ethanol–ethyl acetate–ether, had m. p. 178—180° (Found: N, 10·6. $C_{10}H_{14}O_6N_2$ requires N, 10·8%).

N-(5-*Keto*-L-*pyrrolidine*-2-*carbonyl*)*glycine Ethyl Ester*.—5-Keto-L-pyrrolidine-2-carboxyhydrazide (1 g.; Angier *et al.*, *loc. cit.*) in water was converted into the azide in the usual way. The solution was then added portionwise, with shaking, to a mixture of glycine ethyl ester hydrochloride (1·5 g.), potassium hydrogen carbonate (4·8 g.), and water (7·5 ml.). The reaction mixture was shaken occasionally during the first hour. Next day the solution was saturated with potassium carbonate and extracted with ethyl acetate (3 × 20 ml.). The combined extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The *N*-(5-*keto*-L-*pyrrolidine*-2-*carbonyl*)*glycine ethyl ester* (0·5 g., 33%) soon solidified and was transferred to the filter with a little ethyl acetate; it had m. p. 117—119°, unchanged by recrystallisation from ethyl acetate (Found: C, 50·6; H, 6·9; N, 12·9. $C_9H_{14}O_4N_2$ requires C, 50·5; H, 6·6; N, 13·1%).

N-(5-*Keto*-L-*pyrrolidine*-2-*carbonyl*)*glycine*.—5-Keto-L-pyrrolidine-2-carbonylglycine ethyl ester (0·24 g.) in N-sodium hydroxide (1·20 ml.) was set aside for 2 hours. The product, *N*-(5-*keto*-L-*pyrrolidine*-2-*carbonyl*)*glycine* (0·17 g., 81%), was isolated as described above for the glutamic acid analogue; it had m. p. 157—162°. It was recrystallised from ethanol–ether;

the second (main) fraction had m. p. 162—166° (Found : C, 45·4; H, 5·2; N, 14·6. $C_7H_{10}O_4N_2$ requires C, 45·2; H, 5·4; N, 15·0%).

N-(5-*Keto*-L-*pyrrolidine*-2-*carbonyl*)-L-*tyrosine Ethyl Ester*.—5-Keto-L-pyrrolidine-2-carboxyhydrazide (1 g.) in water was converted into the azide and added to a mixture of L-tyrosine ethyl ester (1.8 g.), potassium hydrogen carbonate (4 g.), ethyl acetate (10 ml.), and dioxan (10 ml.). The reaction mixture was stirred for 2 hours and then left overnight. The aqueous layer was separated and extracted twice with ethyl acetate; the combined ethyl acetate layers were washed with dilute hydrochloric acid and then water, dried (Na_2SO_4), and evaporated under reduced pressure. N-(5-*Keto*-L-*pyrrolidine*-2-*carbonyl*)-L-*tyrosine ethyl ester*, recrystallised from ethyl acetate (yield, 0·35 g.; 16%), had m. p. 132—135°, raised to 133—135° by a further crystallisation (Found : C, 59·8; H, 6·2; N, 8·4. $C_{16}H_{20}O_5N_2$ requires C, 60·0; H, 6·3; N, 8·7%). Hydrolysis gave crude *N*-(5-keto-L-pyrrolidine-2-carbonyl)-L-tyrosine which was difficult to purify and was used in the chromatographic studies below.

Effect of Heating Aqueous Solutions of Pyrrolidone Derivatives.—Aqueous solutions (*ca.* 5%) were kept at 100° for 24 hours and samples then examined by paper partition chromatography using (*a*) phenol saturated with water in an atmosphere containing ammonia, followed by a ninhydrin spray, and (*b*) *n*-butanol saturated with water, acidic products being detected by spraying the paper with a saturated solution of methyl-orange in ethanol–ethyl acetate (1 : 1). In the table, under " (*b*) " are given the R_F values of the spots observed.

	(*a*)			(*b*)	
	Glutamic acid	Glycine	Tyrosine	Before heating	After heating
5-Keto-L-pyrrolidine-2-carboxylic acid ...	+++	—	—	0·46	0·46
5-Keto-L-pyrrolidine-2-carbonyl-L-glutamic acid ...	+	—	—	0·40	0·43
5-Keto-L-pyrrolidine-2-carbonylglycine ...	+	++	—	0·30	0·28 0·44
5-Keto-L-pyrrolidine-2-carbonyl-L-tyrosine	—	—	—	0·66	0·67

Detection of Pyrrolidone Derivatives formed by the Action of Heat on Aqueous Solutions of Glutamyl-peptides.—Aqueous solutions of glutamyl-peptides (approx. 3—5%) were kept at 100° for 24 hours. The products were examined by paper chromotography as above, using butanol and methyl-orange. The R_F values of the products were :

α-L-Glutamylglycine ...	0·31, 0·48	γ-L-Glutamylglycine ...	0·52
α-L-Glutamyl-L-glutamic acid ...	0·44	γ-L-Glutamyl-L-glutamic acid ...	0·52
α-L-Glutamyl-L-aspartic acid ...	0·07, 0·50	γ-L-Glutamyl-L-aspartic acid ...	0·08, 0·47
α-L-Glutamyl-L-tyrosine ...	0·69		
α-L-Glutamyl-L-valine ...	0·71		

Autohydrolysis of α-L-*Glutamyl*-L-*aspartic Acid*.—α-L-Glutamyl-L-aspartic acid (200 mg.) in water (10 ml.) was kept at 100° for 24 hours. The solution was then evaporated to dryness under reduced pressure, and the residue extracted with ethanol and collected (103 mg.). Paper partition chromatography with phenol saturated with water showed the presence of much aspartic acid and some glutamic acid in the residue.

The filtrate was evaporated *in vacuo* and the residue extracted with boiling ethyl acetate (4 × 8 mls.). A syrup remained which did not crystallise. Light petroleum was added to the combined extracts which were left at 0° for some hours and then filtered. The product (10 mg.; m. p. 140—153°) recrystallised from ethyl acetate–light petroleum, whereafter it had m. p. 147—155° (5 mg.), unaltered on admixture with 5-keto-L-pyrrolidine-2-carboxylic acid (Found : C, 46·4; H, 5·4. Calc. for $C_5H_7O_3N$: C, 46·5; H, 5·5%).

Autohydrolysis of α-L-*Glutamyl*-L-*glutamic Acid*.—α-L-Glutamyl-L-glutamic acid (175 mg.) in water (10 ml.) was kept at 100° for 24 hours, then evaporated to dryness under reduced pressure. The residue was extracted several times with boiling ethyl acetate (80 ml. in all), whereafter removal of the solvent left a residue (5 mg.) of m. p. 120—134°. The residue from the extraction was dissolved in hot ethanol, leaving a solid (4 mg.) shown by paper chromatography to contain glutamic acid and a trace of dipeptide.

The ethanolic solution was evaporated under reduced pressure and the residue extracted with boiling ethyl acetate, giving a solid (39 mg., 24%), m. p. 169—179°, raised to 177—180° by recrystallisation from ethanol–ether. The mixed m. p. with 5-keto-L-pyrrolidine-2-carbonyl-L-glutamic acid was 175—178°. The R_F value was 0·42 (5-keto-L-pyrrolidine-2-carbonyl-L-

glutamic acid, 0·42; 5-keto-L-pyrrolidine-2-carboxylic acid, 0·50; both on the same chromatogram).

Autohydrolysis of γ-L-Glutamylglycine.—γ-L-Glutamylglycine (200 mg.) in water (10 ml.) was kept at 100° for 24 hours, then evaporated to dryness under reduced pressure and extracted with ethanol. The residue (62 mg.) showed by paper chromatography the presence of much glycine and some dipeptide or glutamic acid. The filtrate was evaporated to dryness under reduced pressure and the residue extracted several times with boiling ethyl acetate. The combined extracts gave on evaporation 5-keto-L-pyrrolidine-2-carboxylic acid (52 mg.), m. p. 149—155° alone or mixed with the authentic compound, R_F 0·51.

Autohydrolysis of γ-L-Glutamyl-L-glutamic Acid.—γ-L-Glutamyl-L-glutamic acid (200 mg.) in water (10 ml.) was kept at 100° for 24 hours, then evaporated to dryness under reduced pressure. The remaining oil was extracted repeatedly with hot ethyl acetate, to which, after some vacuum-evaporation, was added light petroleum. After storage overnight at 0°, filtration gave 5-keto-L-pyrrolidine-2-carboxylic acid (50 mg.), m. p. 150—156°, unaltered on admixture with the authentic compound, R_F 0·50. The residue from the extractions was stirred with ethanol leaving a white solid (30 mg.). Paper chromatography showed the presence of much glutamic acid and some dipeptide.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 19th*, 1951.]

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107. *The Presence of* cis- *and* trans-3-*Hydroxystachydrine in the Fruit of* Courbonia virgata.

By J. W. CORNFORTH and ALAN J. HENRY.

During the preliminary investigation of the basic constituents of the fruit of *Courbonia virgata* dextro-rotatory forms of both *trans-* and *cis-*3-hydroxystachydrine have been isolated. These compounds form approximately 10% of the dry weight of the husks of the fruit. One of the compounds was also isolated from the kernels, but neither compound has so far been found in the root of the plant.

THE mature fruit of *Courbonia virgata* A. Brongn. contains a single kernel, measuring approximately 15 × 10 × 7 mm. and enclosed in a husk consisting of hard brown epicarp and cream-coloured endocarp. The kernels represent about 80% of the weight of the whole dry fruit. They are free from soluble carbohydrates and contain lower proportions of tetramethylammonium salts and inorganic constituents than do the roots (cf. Henry and Grindley, *J. Soc. Chem. Ind.*, 1949, **68**, 9). These factors would be expected to facilitate isolation of any other basic constituents which might be present. The fruit has a pronounced " fishy " odour which is retained for long periods in a closed vessel. The kernels used in this work were not quite free from tenaciously adhering endocarp.

Extraction of the husk material with ethanol has now given two crystalline, water-soluble, isomeric compounds, m.p. *ca.* 250° and 209—210°, respectively, which we shall distinguish by the suffixes *-a* and *-b* respectively. Similar treatment of the kernels has yielded the former, whereas root material under the same conditions gave only tetramethylammonium nitrate. The presence of L-stachydrine ethyl ester salts in the root has been already established (Henry and King, *J.*, 1950, 2866).

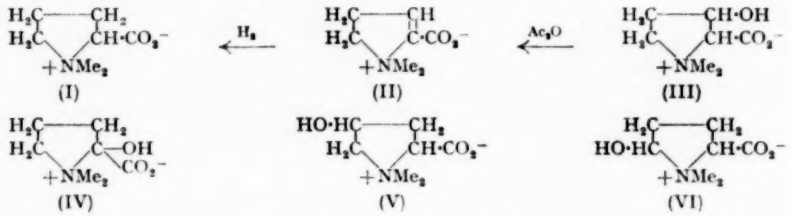
A preliminary examination of the isomer-*a* was made by Dr. H. King, F.R.S. It dissolves readily in water to a neutral, dextrorotatory, non-conducting solution not precipitated by picric acid, sodium picrate, mercuric chloride, iodine in potassium iodide, Tanret's reagent, or by chloroauric or chloroplatinic acid; precipitates are given by phosphotungstic acid and by ammonium reineckate. The hydrochloride and the picrate crystallize readily from ethanol, and the analyses of these and of the original compound-*a* indicate the formula $C_7H_{13}O_3N$. When heated alone, the compound-*a* liberates carbon dioxide and a

vapour which gives a weak pyrrole pine-splinter test; when heated with strong alkali, it liberates a volatile base.

The compound-*b*, of m.p. 209—210°, also affords a neutral, non-conducting aqueous solution, more strongly dextrorotatory than that of its isomer. A crystalline hydrochloride, but no picrate, could be obtained from it.

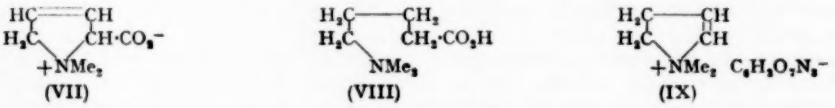
When either isomer is boiled for a short time with acetic anhydride, an optically inactive anhydro-compound, $C_7H_{11}O_2N$, is formed in good yield. Hydrogenation of this in an acidic medium affords DL-stachydrine (I) as the main product. The isomers $C_7H_{13}O_3N$ are therefore hydroxystachydrines and the anhydro-compound is the methyl betaine of a 1-methylpyrroline-2-carboxylic acid. The position of the double bond in the pyrroline was shown by oxidation with cold dilute permanganate; β-dimethylaminopropionic acid was identified as a major oxidation product by the analysis and melting point of its hydrochloride. Hence the anhydro-compound has the structure (II).

The structures (III) and (IV) now come into consideration for the isomers-*a* and -*b*. The latter (IV), however, should be tautomerically unstable, since it is the quaternary salt of a carbinolamine; moreover, both isomers cannot have this structure as they are not enantiomorphs. If it is admitted that migration of a double bond may take place in the formation of the anhydro-betaine, structures (V) and (VI) have to be considered. However, structure (VI) is open to the same objection of tautomeric instability, and structure (V) belongs to the known betaines, turicine and betonicine, neither of which from their properties could be identical or enantiomorphous with our compounds-*a* and -*b*. The latter can therefore be confidently identified as stereoisomerides of 3-hydroxystachydrine (III); provisionally, isomer-*b* might be regarded as a *cis*-form because of its greater solubility and slighter tendency to form crystalline salts. The facile dehydration of the 3-hydroxystachydrines is consistent with their formulation as β-hydroxy-acids.



The 3-hydroxystachydrines-*a* and -*b* must differ in configuration at only one carbon atom, but it is not known whether this is $C_{(2)}$ or $C_{(3)}$ (betonicine and turicine differ at $C_{(2)}$). An attempt to produce $C_{(2)}$-epimers from 3-hydroxystachydrine-*b* by boiling aqueous barium hydroxide, a reagent which racemizes L-stachydrine, gave only the anhydro-compound.

In the hydrogenation product of the anhydro-compound, DL-stachydrine is accompanied by a substance, isolated as the picrate, having the composition of a dimethylaminovaleric acid; and when the hydrogenation is conducted in the absence of added acid this becomes the main product and is apparently accompanied by a little dimethylammonium valerate. Carbon–nitrogen bond hydrogenolysis could hardly take place under these conditions with stachydrine (I) or with the Δ^2-pyrroline (II), but would be normal with the Δ^3-pyrroline (VII) which is an allylammonium ion twice over. Since the structure (VII) is excluded for the anhydro-compound by the oxidation experiment, it seems that a rearrangement (II ⟶ VII) takes place under the influence of the platinum catalyst. In support of this



view is the fact that an unusually long " lag period " has always preceded hydrogenation. The hydrogenolysis product is probably δ-dimethylaminovaleric acid (VIII) rather than the α-isomer.

When 3-hydroxystachydrine-*a* is boiled for some hours with acetic anhydride, carbon dioxide is slowly evolved and from the darkened solution the methopicrate of a methylpyrroline can be prepared. This is presumably 1-methyl-Δ^2-pyrroline methopicrate (IX).

We intend, when the opportunity arises, to study the stereochemistry of the 3-hydroxystachydrines and to attempt their synthesis.

Experimental

Isolation of 3-*Hydroxystachydrines*-a *and* -b *from the Husks.*—The husk material (280 g.), air-dried and ground, was extracted at room temperature with 95% ethanol, first by percolation and then by digestion overnight. The combined extracts (1·8 l.) were allowed to evaporate and the residue was taken up in water (110 c.c.). After acidification with sulphuric acid (3 drops of 2N) and extraction with light petroleum to remove fat, the solution was concentrated, first with gentle heating and later over sulphuric acid in a desiccator. The resulting crystallization was facilitated by frequently breaking the surface crust. Four successive crops (6·1, 3·4, 6·5, 4·8 g.), melting at about 250° (decomp.) and consisting essentially of the isomer-*a*, were obtained in this way, small amounts of cold ethanol being used to wash, and when necessary to collect, the crystals. Further extraction of the husk material with boiling 95% ethanol (500 c.c.) for 3½ hours yielded further material (5·1 g.) of good quality by a similar procedure. The crude material was recrystallized by dissolution in water and concentration as before. After two such treatments, final purification was effected by pouring a concentrated aqueous solution into cold ethanol. 3-*Hydroxystachydrine*-a separated in well-formed colourless prisms, melting with effervescence at about 250° (variable with rate of heating) and having $[\alpha]_D^{20}$ + 10·0° (*c*, 29 in water) (Found: C, 52·9, 52·7; H, 8·1, 8·2; N, 8·9, 9·0. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%). The yellow *picrate* separated readily from ethanol; it had m. p. 160° (Found: C, 40·2; H, 4·1; N, 14·1, 14·6. $C_7H_{13}O_3N,C_6H_3O_7N_3$ requires C, 40·2; H, 4·1; N, 14·4%). The *hydrochloride* crystallized from ethanol in needles, m. p. 196—197° (decomp.), not hygroscopic (Found: N, 7·5. $C_7H_{13}O_3N,HCl$ requires N, 7·2%).

The mother-liquor from the final crop of crude 3-hydroxystachydrine-*a* was allowed to dry over sulphuric acid. After 10 days the viscous, crystal-bearing matrix was filtered without addition of ethanol and sucked as free as possible from mother-liquor. The crude crystals were dissolved in water (10 c.c.) and the solution, after treatment with charcoal (0·3 g.) and filtration, was allowed to evaporate at room temperature to small bulk. The residue was cooled in a refrigerator and stirred with ethanol (5 c.c.); the resultant large crystals were collected, washed with cold ethanol (10 c.c.), and air-dried (2·46 g.). This product had m. p. 210—212° (decomp.) after drying at 110°. It was dissolved in water and the filtered solution was concentrated to 5 c.c., poured into cold ethanol (25 c.c.), and left in the refrigerator. Next day the colourless prisms of 3-*hydroxystachydrine*-b *monohydrate* (1·87 g.), m.p. 209—210° (decomp.), $[\alpha]_D^{22}$ + 53° (*c*, 2·5 in water), were collected, washed with ethanol and then acetone, and air-dried (Found: N, 8·0; loss at 100—110°, 10·4, 10·45. $C_7H_{13}O_3N,H_2O$ requires N, 7·9; H_2O, 10·2%. Found, on dried material: C, 53·3; H, 8·0; N, 9·4%). The *hydrochloride* crystallized from dry ethanol in prisms, m.p. 201—202° (decomp.) (Found: N, 7·0%). The mother-liquors from the crude 3-hydroxystachydrine-*b* contained 19 g. of solids which will be further investigated.

Isolation of 3-*Hydroxystachydrine*-a *from the Kernels.*—The ground material was extracted (Soxhlet) with light petroleum, and the residue (810 g.) digested twice with ethanol at room temperature. The combined ethanol extracts (2 l.) were allowed to evaporate. An aqueous solution of the residue, after exhaustive extraction with light petroleum and with ether–chloroform, was allowed to evaporate, finally over calcium chloride. Ethanol (10 c.c.) was stirred into the viscous, partly crystalline mass before filtration, which was very slow. The residue, after being washed with ethanol, was dissolved in water and the solution evaporated to small bulk after treatment with charcoal. The well-formed crystals of 3-hydroxystachydrine-*a* (4·0 g.) were collected and washed with alcohol, and had m.p. 248—250° (decomp.). The mother-liquor contained 30 g. of solids which are being further studied.

Examination of the Root Material.—Dried and ground root (1 kg.), previously extracted with light petroleum and with chloroform, was digested twice with ethanol (1400 c.c) at room temperature. The extract was allowed to evaporate and the residue was dissolved in water. The filtered solution, after extraction with light petroleum and then with ether–chloroform, was examined for extractable bases by being made alkaline and extracted with ether–chloroform; it was then acidified and concentrated, finally over sulphuric acid, to a viscous mass containing crystals. The latter were collected by means of ethanol, dissolved in water (10 c.c.),

treated with charcoal, and recovered by evaporation to small bulk and addition of ethanol (3 c.c.). The product (1·46 g.) has been identified as tetramethylammonium nitrate. There is no evidence at present for the presence of either of the 3-hydroxystachydrines in the root of *Courbonia virgata*.

Action of Acetic Anhydride on the 3-*Hydroxystachydrines*.—3-Hydroxystachydrine-*a* (1·568 g.) was boiled with acetic anhydride (8 c.c.) until dissolution was complete (a few minutes). The solution was concentrated at low pressure and water was added; after the remaining acetic anhydride had reacted, the mixture was evaporated once or twice at low pressure with addition of ethanol. The crystalline residue was taken up in a little ethanol; pyridine (1 c.c.) was added, and then ethyl acetate to incipient turbidity. The crystalline, nearly pure 1 : 1-*dimethyl*-Δ^2-*pyrrolinium*-2-*carboxylic betaine* (II) (1·088 g.) was collected next day. Recrystallization from ethanol–ethyl acetate gave well-formed prisms, m.p. about 235° (decomp.; variable). The substance was hygroscopic; an aqueous solution was neutral and showed no detectable optical activity (Found: C, 59·6; H, 8·1; N, 10·4. $C_7H_{11}O_2N$ requires C, 59·6; H, 7·8; N, 9·9%). The *picrate* separated from ethanol in stout, four-sided yellow prisms, m.p. 174—175° (Found: C, 42·0; H, 3·6; N, 14·6. $C_7H_{11}O_2N, C_6H_3O_7N_3$ requires C, 42·2; H, 3·8; N, 15·1%). When pyridine was omitted in the initial crystallization of the pyrroline-betaine, a crystalline mixture of it and its acetate separated.

3-Hydroxystachydrine-*b* on similar treatment with acetic anhydride gave the anhydro-compound in substantially the same yield. The picrate had m.p. 174—175° alone or mixed with the previous specimen (Found: C, 41·8; H, 3·8; N, 15·3%). The anhydro-compound was isolated in good yield as the picrate after 3-hydroxystachydrine-*b* (500 mg.) had been boiled with barium hydroxide (1 g.) in water (20 c.c.) for 3 hours. The reaction mixture then showed no optical activity.

3-Hydroxystachydrine-*a* (159 mg.) was heated (bath, 150°) with acetic anhydride (1 c.c.) in a slow current of nitrogen. Carbon dioxide was detected in the emergent gas by passing it through aqueous barium hydroxide. After about 3 hours the acetic anhydride was removed at low pressure and ethanolic picric acid was added to the residue. One crystallization from methanol and two from ethanol (much tar had to be separated) gave deep yellow long prismatic needles (30 mg.), m.p. 284° (decomp.; in bath at 280°) of 1 : 1-*dimethyl*-Δ^2-*pyrrolinium picrate* (IX) (Found: C, 43·8; H, 4·6; N, 17·2. $C_6H_{12}N, C_6H_2O_7N_3$ requires C, 44·2; H, 4·3; N, 17·2%).

Hydrogenation of the Anhydro-compound.—The anhydro-compound (300 mg.) in hydrochloric acid (5 c.c.; N) with platinum oxide (18 mg.) was shaken with hydrogen at atmospheric temperature and pressure. After reduction of the catalyst further absorption of hydrogen did not begin for some minutes. Thereafter the uptake was rapid until 1·1 mols. had reacted; the catalyst then coagulated and absorption ceased (this sequence of events has been observed repeatedly in this reduction). The solution was filtered and evaporated at low pressure. Aqueous sodium picrate (12 c.c.; 4·3%) was added to the residue; the mixture was evaporated at low pressure and the solid collected with the help of a little water. The dried product was boiled with ethyl acetate, an orange residue remaining undissolved. This appeared to be a stachydrine picrate containing less than one equivalent of picric acid: on recrystallization from ethanol four-sided orange leaflets were obtained, having m.p. 194—195° depressed to 180° on admixture with DL-stachydrine picrate (Found: C, 45·2; H, 4·7; N, 14·0%). However, when this substance was recrystallized from ethanol containing picric acid, yellow leaflets, m.p. and mixed m.p. 195°, of DL-stachydrine picrate were obtained (Found: C, 41·7; H, 4·3; N, 14·6. Calc. for $C_7H_{13}O_2N, C_6H_3O_7N_3$: C, 41·9; H, 4·3; N, 15·1%).

The ethyl acetate extract after concentration deposited prisms which were recrystallized from alcohol to give yellow acicular prisms, m.p. 153—154°, of (?) *δ-dimethylaminovaleric acid picrate* (Found: C, 41·4; H, 5·1; N, 14·5. $C_7H_{15}O_2N, C_6H_3O_7N_3$ requires C, 41·7; H, 4·8; N, 15·0%).

When the anhydro-compound was hydrogenated in the absence of hydrochloric acid the uptake of hydrogen was greater and the picrate, m.p. 153—154°, was the only product isolated. The solution smelled of valeric acid when acidified and of a volatile amine, presumably dimethylamine, when made alkaline.

Oxidation of the Anhydro-compound.—The anhydro-compound (0·5 g.) in a little water was cooled to 0° and treated slowly with 4% aqueous potassium permanganate. After addition of 50 c.c. the initially rapid reaction became slower; the process was interrupted after addition of a further 10 c.c. The filtered solution was acidified with hydrochloric acid and evaporated at low pressure. The residue was extracted with cold ethanol. Evaporation of the ethanol left a crystalline residue which was recrystallized from ethanol and formed leaflets (115 mg.),

m.p. about 175°. Three more recrystallizations raised the m.p. to 187—188° (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571, give m.p. 188—191° for β-dimethylaminopropionic acid hydrochloride) (Found: C, 39·1; H, 7·4; N, 9·1. Calc. for $C_5H_{11}O_2N,HCl$: C, 39·1; H, 7·8; N, 9·1%). The m.p. was strongly depressed by admixture with dimethylaminoacetic acid hydrochloride.

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108. *The Isolation of* L-*Stachydrine from the Fruit of* Capparis tomentosa.

By J. W. CORNFORTH and ALAN J. HENRY.

L-Stachydrine has been isolated in substantial amount from the pericarp, endocarp, and seed husk of the fruit of *Capparis tomentosa* Lam.

IN view of the reputed toxicity to camels of *Capparis tomentosa* Lam. (family Capparidacæ) the fruits of the shrub have been examined for the presence of basic constituents analogous to those previously found (Henry, *Brit. J. Pharmacol.*, 1948, **3**, 187; Henry and Grindley, *J. Soc. Chem. Ind.*, 1949, **68**, 9; Henry and King, *J.*, 1950, 2866; Cornforth and Henry, preceding paper) in the various parts of *Courbonia virgata* A. Brongn., of the same family. *Capparis tomentosa* Lam. is a climbing shrub, the dry, mature fruit of which consists of a hard spherical pericarp 1—2½ inches in diameter, containing a friable pulpy endocarp in which is embedded a number of seeds consisting of a kernel about 10 × 8 × 5 mm. each in a separate seed husk (testa). The husks and pulp were examined separately, during the course of which no evidence could be found for the presence of volatile amines, extractable alkaloids, tetramethylammonium hydroxide or 3-hydroxystachydrine-*a* or -*b*. However, purified extracts gave a heavy precipitate of globules on treatment with iodine solution. A number of periodide fractions were obtained by stepwise precipitation, first in neutral and then in acid solution. All these, however, proved to be of similar nature and to consist essentially of L-stachydrine periodide.

L-Stachydrine has been isolated as both hydrochloride and picrate in high purity, and the constants found for these salts are perhaps more accurate than previously published data. The sample obtained by Steenbock (*J. Biol. Chem.*, 1918, **35**, 1) was evidently partly racemised, perhaps by the barium hydroxide used in the isolation process. On the other hand the data of Yoshimura and Trier (*Z. physiol. Chem.*, 1912, **77**, 301) agree well with our own, except that the rotation of their hydrochloride and the melting point of their picrate are somewhat lower. A synthetic specimen of L-stachydrine hydrochloride was prepared from L-proline, silver oxide, and methyl iodide in methanol. This method was chosen as being unlikely to induce racemisation. The product corresponded in melting point and optical rotation to the specimen from *Capparis tomentosa*.

From the pericarp material, L-stachydrine hydrate was isolated in considerable quantity, purification through a salt being here unnecessary. Some physical properties of this substance are reported for the first time.

EXPERIMENTAL

Extraction of Seed Husk and Pulp.—Husk (500 g.) and pulp (1000 g.) materials, separated as completely as possible from each other, were dried and ground, then twice digested overnight in the cold with ethanol with occasional shaking. The combined ethanol extracts were evaporated at atmospheric temperature with an intermediate filtration to remove separated fat, then diluted with a little water and exhaustively extracted with light petroleum. The aqueous solutions were evaporated at atmospheric temperature to thick syrups, but from neither of them did crystals separate, suggesting absence of the 3-hydroxystachydrines isolated from the husks of *Courbonia virgata*. After suitable dilution the extracts, which were acid in reaction,

were exhaustively extracted with chloroform–ether, then made just alkaline with sodium carbonate and again extracted with chloroform–ether. These operations showed absence of volatile amines and of extractable alkaloids. The extracts were next treated with neutral lead acetate until the solutions became acid followed by basic lead acetate until there was no further precipitation, and excess of lead was removed from the filtrates with hydrogen sulphide. The extracts were again evaporated to thick syrups, but no crystallisation occurred.

Precipitation of Periodides.—The extracts were diluted to 200 c.c. after neutralisation with excess of calcium carbonate and filtration of the excess, and 150 c.c. of each solution treated in distillation flasks of 300 c.c. capacity with iodine solution (9% iodine in 10% ammonium iodide, 50 c.c.) at atmospheric temperature. The solutions were refrigerated for 4 days by which time the precipitated globules of periodide had largely crystallised. Chloroform was added to the flasks through a long-stemmed funnel until the whole of the mother-liquor had been floated out through the side-tube of the flask. After decantation of the chloroform the periodide residues were treated with ethanol (2 c.c.), then with successive small quantities of amyl alcohol until the periodide had only low solubility in it. The periodide residues were transferred to sintered-glass funnels, washed with amyl alcohol, and air-dried. The pulp extract yielded 2·92 g. of solid periodide and the husk extract yielded 3·18 g., m. p. (of both) 230° (decomp.). These periodides were decomposed to hydriodides by treatment with water, then converted into hydrochlorides by being shaken with the freshly precipitated silver chloride. The hydrochloride solutions were evaporated to dryness, dissolved in absolute ethanol, and filtered, then the hydrochlorides recrystallised from water after removal of the ethanol. M. p. (220°) and mixed m. p. showed the two hydrochlorides to be identical. The amyl alcohol wash-liquors were washed with water in the hope of freeing them from ammonium salts and other impurities, but it was found that the L-stachydrine hydriodide was extracted by the water more readily than was ammonium iodide.

The mother-liquors from the first periodide precipitates were further treated with three successive quantities (50, 50, and 100 c.c.) of iodine solution. The periodide fractions so obtained proved to be essentially similar to the first periodide crops, though they tended to become more fluid and more soluble in amyl alcohol, probably as a result of the greater excess of iodine tending to precipitate a higher periodide. Crystals of periodide formed with a limited amount of iodine have been found to become fluid on addition of excess of free iodine.

After separation of the fourth crops of periodide from the neutral solutions, these were acidified by addition of concentrated hydrochloric acid (20 c.c.). Each solution yielded a substantial precipitate of fluid periodide which was isolated as before. These periodides were reduced to hydriodides, first by treatment with water, then by being shaken with silver powder, and the hydriodides converted into hydrochlorides by being shaken with excess of silver chloride. Preliminary examination having shown that the hydrochlorides from the two solutions were identical, these were combined and evaporated to very low bulk and the crystallised hydrochloride was isolated; it had m. p. 220° alone or mixed with the hydrochlorides described above. A further crop of crystals also proved to be identical with the first crop, and the residual mother-liquor on suitable treatment with picric acid yielded a substantial crop of a picrate which was identical with that prepared from the hydrochloride.

Properties of Hydrochloride and Picrate.—Hydrochloride fractions of good quality from both neutral and acid precipitation were combined (6 g.) and recrystallised from hot absolute ethanol. The crystals, stout needles $\frac{1}{2}$—1 inch long, were washed with cold 1 : 1 ethanol–acetone and oven-dried to constant weight. They were anhydrous and non-hygroscopic. The yield was 3·85 g., the m. p. 222° with rapid evolution of gas (Found: C, 46·8; H, 7·9; N, 7·9. Calc. for $C_7H_{14}O_2NCl$: C, 46·8; H, 7·8; N, 7·8%), and $[\alpha]_D^{20}$ was −28·1° (*c*, 4·82 in water) which is significantly higher than previously published figures (Yoshimura and Trier, *loc. cit.*, give $[\alpha]_D^{18}$ −26·2°). A further quantity (1·65 g.) was obtained from the mother-liquor.

The picrate could be prepared by addition of saturated aqueous picric acid solution to a solution of the hydrochloride and evaporation to smaller bulk at atmospheric temperature. It crystallised from water in stout hexagonal prisms, m.p. 199—200° without appreciable decomposition, since the solidified melt remelted at 199—200°.

Synthesis of L-*Stachydrine Hydrochloride.*—L-Proline (1 g.) was added to a suspension of silver oxide (2 g.) in methanol (20 c.c.). When formation of a silver compound appeared complete, methyl iodide (2 c.c.) was added. Evolution of heat and separation of silver iodide were noticed at once. Next day a little more methyl iodide was added and the mixture heated for 3 hours (reflux). The neutral solution was filtered and evaporated at low pressure. To the crystalline residue concentrated hydrochloric acid (1 c.c.) was added. Water was removed by

evaporation with ethanol. The product after two recrystallisations from ethanol gave handsome prisms, m. p. 222° (decomp.) alone or mixed with the above hydrochloride, $[\alpha]_D^{22}$ −27·5° (*c*, 2 in water) (Found: C, 46·8; H, 7·6; N, 7·9%).

Racemisation of the C. tomentosa *Product.*—To confirm the identity of this product with L-stachydrine hydrochloride a sample (241 mg.) was boiled in water (20 c.c.) with barium hydroxide (1 g.) for 5 hours. The barium was precipitated with sulphuric acid and the filtered solution, which was optically inactive, evaporated. From the residue a picrate (yellow plates, m. p. 195—196°, from ethanol) and an oxalate (needles, m. p. 105—107°, from ethanol) were prepared. These correspond to the DL-stachydrine derivatives reported by Schulze and Trier (*Z. physiol. Chem.*, 1910, **67**, 73). The racemisation with barium hydroxide is mentioned by Yoshimura and Trier (*loc. cit.*).

Extraction of Pericarp.—Dry, ground pericarp material (1 kg.) was exhaustively extracted with cold alcohol. The solvent was removed at room temperature and the residue mixed with water. After removal of fat and treatment with lead acetate and hydrogen sulphide as described above, the aqueous solution was allowed to evaporate, finally *in vacuo* over calcium oxide. After some months the partly crystalline mixture (34 g.) was filtered, leaving a solid (5·7 g.) (A) which was purified by crystallisation from water (three crops, total 3·3 g.), followed by dissolution in a little ethanol and addition of chloroform (200 c.c.). The chloroform solution, after decantation from a little resin, was evaporated. The residue on recrystallisation from cold ethanol gave impure material (1·09 g.). By repeated extraction of the evaporated ethanolic mother-liquors with hot chloroform and evaporation to small bulk, L-stachydrine hydrate (1·56 g.) was obtained in hexagonal crystals, m. p. 116—118° (partial melting; in bath at 112°), $[\alpha]_D^{24\cdot5}$ −40·25° (*c*, 4 in water) (Found: loss *in vacuo* over sulphuric acid, 11·4; N, 8·2. Calc. for $C_7H_{13}O_2N,H_2O$: H_2O, 11·2; N, 8·7%). The dehydrated material had m. p. 232° (in bath at 230°) with little darkening. A saturated solution of the hydrate in chloroform at 23° contained approximately 28 mg./ml. The hydrate afforded L-stachydrine picrate, m. p. and mixed m. p. 199—200°, on treatment with picric acid. The hydrate was stable to the air in Khartoum, but deliquescent in the moist air of London. Schulze and Trier (*loc. cit.*) reported that DL-stachydrine hydrate is deliquescent and insoluble in cold chloroform.

The mother-liquor from (A) was extracted ten times with boiling chloroform–ethanol (chloroform, 150 c.c.; ethanol, 5 c.c.). The extracts, filtered hot, were united and evaporated; this gave crude crystals (12·5 g.) which afforded nearly pure L-stachydrine hydrate (5·9 g.) on recrystallisation from cold water.

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109. *Tropolones. Part IV.* The Preparation of αβ-Benzotropolone.*

By J. W. COOK, A. R. M. GIBB, R. A. RAPHAEL, and A. R. SOMERVILLE.

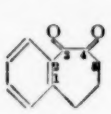
Direct dehydrogenation of benzo*cyclo*heptene-3 : 4-dione (I) with palladium–charcoal gives a small yield of αβ-benzotropolone (III; X = H). A better method consists of the bromination of (I) and hydrogenolysis of the resulting α′-bromo-αβ-benzotropolone. Some properties of αβ-benzotropolone are recorded.

THE first rational synthesis of a tropolone was reported by Cook and Somerville (*Nature*, 1949, **163**, 410) who described the direct dehydrogenation of benzo*cyclo*heptene-3 : 4-dione (I) to αβ-benzotropolone. Since then the intensity of the investigations on the monocyclic tropolones has led to neglect of this benzo-derivative, although the method used for its preparation has meanwhile been fruitfully employed by other investigators to obtain derivatives of the parent compound, *e.g.*, purpurogallin (Caunt, Crow, Haworth, and Vodoz, *J.*, 1950, 1631; 1951, 1313; Barltrop, Johnson, and Meakins, *J.*, 1951, 181). For the sake of completeness, therefore, the present communication describes in detail the

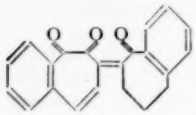
* Part III, *J.*, 1951, 2244.

original preparation of αβ-benzotropolone, together with a much superior modification, and records some properties of the product.

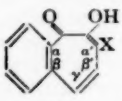
Dehydrogenation of the dione (I) in boiling trichlorobenzene in the presence of palladium–charcoal gave a small yield (16%) of the desired αβ-benzotropolone (III; X = H). In addition a higher-melting by-product was obtained which was not a tropolone. The analytical results for this compound suggest that its constitution may be represented by (II) derived by an aldol-like condensation between two molecules of the dione (I) and subsequent partial dehydrogenation. The paucity of the yield in this procedure encouraged



(I)



(II)



(III)

an alternative approach, and the success of the bromination–dehydrobromination reaction for the preparation of tropolone itself (Part I, *J.*, 1951, 503) suggested its application in this case. When the dione (I) was treated in acetic acid with 2 mols. of bromine and allowed to stand at room temperature a fair yield (49%) of very pure α′-bromo-αβ-benzotropolone (III; X = Br) crystallised from the reaction mixture. In some preparations two by-products were encountered. The first, obtained in minute yield, consisted of benzotropolone itself; the other, from its general chemical characteristics and analytical data, was almost certainly 5-bromobenz*ocyclo*heptene-3 : 4-dione. Bromobenzotropolone readily formed a sodium salt but the insolubility of the latter rendered it unsuitable for hydrogenolysis by the procedure described for tropolone (Part I). It was found, however, that hydrogenolysis proceeded smoothly in ethanolic solution containing an excess of triethylamine to give a good yield (68%) of pure αβ-benzotropolone. The overall yield (34%) from this two-step procedure shows the marked advantage over the direct dehydrogenation method.

αβ-Benzotropolone possessed all the properties now familiar for this class of compound (Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99). It was devoid of carbonyl reactivity, gave a red ferric colour, and a chloroform-soluble copper salt, coupled with diazonium salts, and dissolved in caustic alkali solutions; unlike tropolone, however, it was insoluble in sodium hydrogen carbonate solution and this lower acidity is reflected in its higher p*K* value (*ca.* 9·5; a more precise value could not be obtained because of the insolubility of the compound). A solid 3 : 5-dinitrobenzoate and sub-picrate were obtained but the acetate was a liquid. Even in the presence of methanol ethereal diazomethane reacted only very sluggishly with αβ-benzotropolone, to give a small yield of oily methyl ether with recovery of most of the starting material. Methylation with methyl toluene-*p*-sulphonate yielded an oil; on treatment with alcoholic 2 : 4-dinitrophenylhydrazine sulphate this product gave a red, solid derivative the analysis of which was compatible with the formulation of the compound as the 2 : 4-dinitrophenylhydrazone of αβ-benzotropolone methyl ether.

The skeletal structure of αβ-benzotropolone was proved by catalytic hydrogenation to a mixture of *cis*- and *trans*-benz*ocyclo*heptene-3 : 4-diols, oxidative fission of which gave the known γ-*o*-carboxyphenylbutyric acid. In a manner exactly analogous to that obtaining in the case of tropolone itself, αβ-benzotropolone underwent degradative fission on being treated with alkaline hydrogen peroxide, to yield *o*-carboxycinnamic acid. It is noteworthy that the aromatisation of colchiceine to *N*-acetylcolchinol by this reagent (cf. Part I) has not yet been paralleled by any other tropolone derivative. On being fused with potassium hydroxide αβ-benzotropolone behaved typically, to give a good yield of α-naphthoic acid.

Treatment of αβ-benzotropolone in acetic acid with 1 mol. of bromine gave a good yield of a monobromo-derivative which proved to be identical with the bromo-αβ-benzotropolone obtained by the bromination of the dione (I). Its constitution was not rigidly established but by analogy it is almost certainly the α′-bromo-compound (III; X = Br) (cf. Part III, *J.*,

1951, 2244). Further bromination of this product readily gave dibromo-αβ-benzotropolone, most probably the α′γ-derivative.

βγ-Benzotropolone, the position isomer of the compound described above, has been prepared by a Thiele-type condensation between *o*-phthalaldehyde and acetol (Tarbell, Scott, and Kemp, *J. Amer. Chem. Soc.*, 1950, **72**, 379) and the properties of this substance, insofar as they have been examined, resemble to a considerable degree those of the αβ-isomer. In particular it is noteworthy that a 2 : 4-dinitrophenylhydrazone was obtained from the phenyl ether.

Since this work was completed, Nozoe, Kitahara, and Andô (*Proc. Japan Acad.*, 1951, **27**, 107) have briefly reported some substitution products of αβ-benzotropolone. Their results are partly at variance with ours. In particular, they claim that αβ-benzotropolone is converted by diazomethane into its methyl ether, m. p. 82·5—83·5°, to which they ascribe the erroneous formula $C_{12}H_{11}O_2$. Our own results suggest that this is essentially unchanged benzotropolone (see above).

Experimental

*Benzocyclo**heptene*-3 : 4-*dione* (I).—A solution of selenium dioxide (10·5 g.) in ethanol (80 c.c.) was added dropwise during 4 hours to a boiling solution of benzo*cyclo*hepten-3-one (15 g.) (prepared by Plattner's method, *Helv. Chim. Acta*, 1944, **27**, 804) in ethanol (30 c.c.) and heating was continued for a further 2 hours. The cooled, filtered solution was evaporated to dryness and the residual oil fractionated under reduced pressure; after a small fore-run of unchanged starting material (0·6 g.), benzo*cyclo*heptene-3 : 4-dione (13 g.) was obtained as a yellow oil, b. p. 128—132°/0·4 mm., solidifying on long storage to yellow prisms, m. p. 45—49°. The *mono*-2 : 4-*dinitrophenylhydrazone* crystallised from *n*-butanol in yellow needles, m. p. 232—234° (Found: C, 57·5; H, 3·95; N, 15·8. $C_{17}H_{14}O_8N_4$ requires C, 57·6; H, 3·95; N, 15·8%). The dione did not form a quinoxaline on treatment with alcoholic *o*-phenylenediamine.

Fission of the dione with alkaline peroxide in the cold produced a high yield of γ-*o*-carboxyphenylbutyric acid, crystallising from water and benzene–light petroleum in needles, m. p. 138—139° (Found: C, 64·0; H, 6·3. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8%) (Hückel and Goth, *Ber.*, 1924, **57**, 1289, give m. p. 139—140°).

α′-*Bromo*-αβ-*benzotropolone* (III; X = Br).—To a stirred solution of benzo*cyclo*heptene-3 : 4-dione (10 g.) in glacial acetic acid (10 c.c.) was added slowly a solution of bromine (19·8 g., 2 mols.) in glacial acetic acid (20 c.c.), and the resulting solution set aside for 4 days at room temperature. The separated crystalline mass was filtered off, and the mother-liquors were diluted with acetic acid (10 c.c.) and heated to 60° for 3 hours, whereby a further small crop of crystals was obtained. The combined product was crystallised from glacial acetic acid; α′-*bromo*-αβ-*benzotropolone* (7 g., 49%) formed stout yellow prisms, m. p. 143—144° (Found: C, 52·5; H, 2·9; Br, 31·85. $C_{11}H_7O_3Br$ requires C, 52·6; H, 2·8; Br, 31·8%). The compound gave a deep red ferric reaction, a green amorphous copper salt, a bright yellow, sparingly soluble sodium salt, and a maroon precipitate with toluene-*p*-diazonium chloride. Treatment with ethereal diazomethane gave the *methyl ether*, m. p. 84—85° (Nozoe *et al.*, *loc. cit.*, give 65—68°), crystallising in colourless, feathery needles from light petroleum (b. p. 60—80°) (Found: C, 54·3; H, 3·4. $C_{12}H_9O_2Br$ requires C, 54·35; H, 3·4%).

In one experiment a small quantity of crystalline by-product was obtained which crystallised from *cyclo*hexane in colourless plates, m. p. 92—94° (Found: C, 52·15; H, 3·55; Br, 31·55. $C_{11}H_9O_2Br$ requires C, 52·15; H, 3·55; Br, 31·6%). The compound reacted readily with pyridine and dimethylamine, to give tars and gave a yellow precipitate on treatment with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. These data indicate the compound to be 5-*bromo*-*benzo*cyclo*heptene*-3 : 4-*dione*.

αβ-*Benzotropolone* (III; X = H).—(*a*) A solution of the dione (I) (3·2 g.) in 1 : 2 : 4-trichlorobenzene (20 c.c.) was heated under reflux under nitrogen with palladium–charcoal (2 g.; 10%) for 8 hours. Acidic impurities were removed from the filtered solution by washing it with sodium hydrogen carbonate solution, and the organic layer was then shaken with potassium hydroxide solution. An insoluble, crystalline precipitate formed was filtered off and crystallised from glacial acetic acid, to give pale yellow prisms, m. p. 270—271° (Found: C, 80·5; H, 5·05. $C_{22}H_{16}O_3$ requires C, 80·5; H, 4·9%). This condensation *product* (II) gave a bright orange colour with concentrated sulphuric acid but no ferric colouration.

The bright yellow aqueous alkaline extract was acidified and extracted with ether. Drying and evaporation gave a gummy residue which was extracted with boiling *cyclo*hexane; evapor-

ation of the extract to crystallising point gave αβ-*benzotropolone* (0·5 g.) as pale yellow needles, m. p. 85—86°, subliming at 65—70°/0·05 mm. [Found: C, 76·5; H, 4·65%; *M* (Rast), 186. $C_{11}H_8O_2$ requires C, 76·7; H, 4·7%; *M*, 172]. Microhydrogenation with palladium in glacial acetic acid gave $\equiv$ 3·1; with platinic oxide $\equiv$ 7·3 were revealed. Light absorption in ethanol: $\lambda_{max.}$ in mμ (log ε); 237 (4·45), 260 (4·35), 343 (3·9). $\lambda_{infl.}$ in mμ (log ε); 268 (4·26), 332 (3·85). A plateau was exhibited at 373—388 mμ (3·83). The compound gave a blood-red ferric colour, a resinous crimson precipitate with toluene-*p*-diazonium chloride and an olive-green copper salt crystallising in needles, m. p. 249—250°, from chloroform; it dissolved in concentrated hydrochloric acid, to give a bright yellow solution from which it could be recovered unchanged by dilution with water. The 3 : 5-*dinitrobenzoate*, prepared in poor yield by the usual procedure, crystallised in colourless plates, m. p. 174—175°, from ethanol or benzene–light petroleum (Found: C, 59·05; H, 3·0. $C_{18}H_{10}O_7N_2$ requires C, 59·0; H, 2·75%). The *sub-picrate*, m. p. 63—64°, crystallised from ethanol in orange prisms [Found: C, 58·7; H, 3·55; N, 7·35. $(C_{11}H_8O_2)_2,C_6H_3O_7N_3$ requires C, 58·65; H, 3·3; N, 7·35%].

With hot acetic anhydride αβ-benzotropolone formed the oily acetate, readily hydrolysable to the parent compound by dilute sodium hydroxide. Treatment with ethereal diazomethane resulted in no perceptible nitrogen evolution and even after 24 hours in the presence of methanol much unchanged αβ-benzotropolone was recovered. Methylation with methyl toluene-*p*-sulphonate (1 mol.) in aqueous alcoholic sodium hydroxide gave an oil which solidified at −15° but remelted at 0°. On being heated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate this ether yielded a 2 : 4-*dinitrophenylhydrazone* crystallising from ethyl acetate in small red prisms, m. p. 242—243° (Found: C, 58·4; H, 3·7; N, 15·3. $C_{18}H_{14}O_5N_4$ requires C, 59·0; H, 3·85; N, 15·3%).

(*b*) A solution of bromobenzotropolone (5·8 g.) and triethylamine (6 c.c.) in ethanol (50 c.c.) was shaken under hydrogen at room temperature and pressure in the presence of palladium–charcoal (10%; 500 mg.). Absorption slackened after the smooth uptake of 1 mol. of hydrogen. Removal of the catalyst and solvent left a residue which was made distinctly acid by the addition of dilute sulphuric acid. The resulting solid was filtered off, dried, and purified by sublimation; crystallisation from *cyclo*hexane gave αβ-benzotropolone, m. p. 85—86° (2·75 g., 68%).

Hydrogenation of αβ-Benzotropolone.—A solution of benzotropolone (50 mg.) in ethanol (20 c.c.) was shaken with hydrogen in the presence of platinic oxide (5 mg.) until 3 mols. of hydrogen were absorbed. Removal of catalyst and solvent, followed by trituration of the residue with *cyclo*hexane, gave a pale yellow solid (40 mg.) which was purified by crystallisation from light petroleum and then water. The resulting mixture of *cis*- and *trans*-benzo*cyclo*heptene-3 : 4-diol crystallised in white prisms, m. p. 110—123° (Found: C, 74·3; H, 7·85. Calc. for $C_{11}H_{14}O_2$: C, 74·15; H, 7·9%); it gave a yellow-green colour with potassium tetramethylosmate. Oxidation of the diol with excess of warm potassium hypobromite solution gave, after acidification, γ-*o*-carboxyphenylbutyric acid, m. p. and mixed m. p. 136—138°.

Oxidation of αβ-Benzotropolone.—A solution of benzotropolone (200 mg.) in hot sodium hydroxide solution (5 c.c.; 0·5N) was cooled and the resulting deep yellow suspension of sodium salt treated with hydrogen peroxide (0·3 c.c.; 30%). After 36 hours a colourless solution was formed; acidification and extraction with ether yielded a colourless solid (60 mg.), crystallising from aqueous acetic acid in prisms, m. p. 186—188°, remelting after solidification at 146—148°. These m. p. were unchanged on admixture with authentic *o*-carboxycinnamic acid which is transformed at its m. p. into the lactone of β-hydroxy-β-*o*-carboxyphenylpropionic acid (phthalideacetic acid) (Titley, *J.*, 1928, 2576).

Bromination of αβ-Benzotropolone.—A solution of benzotropolone (100 mg.) in glacial acetic acid (5 c.c.) was treated dropwise with bromine (100 mg., 1·1 mols.) in acetic acid (0·5 c.c.). A yellow oil separated, which redissolved with evolution of hydrogen bromide when the solution was warmed. Evaporation to dryness followed by crystallisation of the residue from acetic acid gave α′-bromobenzotropolone (III; X = Br) (90 mg.), m. p. 143—145° alone or admixed with the bromination product of benzo*cyclo*heptene-3 : 4-dione (Nozoe *et al.*, *loc. cit.*, give 148—149°).

A solution of bromobenzotropolone (100 mg.) in acetic acid (5 c.c.) was similarly treated with bromine (200 mg.) in acetic acid (1 c.c.) and the solution heated under reflux for 30 minutes. Evaporation and crystallisation of the residue from acetic acid gave α′γ-*dibromobenzotropolone* (120 mg.) in silky, yellow needles, m. p. 119—121° (Found: C, 40·0; H, 1·95. $C_{11}H_6O_2Br_2$ requires C, 40·0; H, 1·85%).

α-*Naphthoic Acid.*—αβ-Benzotropolone (26 mg.) was treated with potassium hydroxide solution (80%; 1 c.c.), and the mixture heated to 180—185° at which temperature it was kept

for 30 minutes. The cooled melt was dissolved in water and then acidified, and the voluminous precipitate (20 mg.) crystallised from aqueous alcohol, to give α-naphthoic acid, m. p. 156—160° (m. p. 159—161° on admixture with an authentic specimen of m. p. 160—162°).

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THE UNIVERSITY, GLASGOW, W.2. [*Received, October 22nd,* 1951.]

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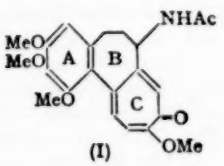
110. *Colchicine and Related Compounds. Part XII.* Some Molecular Rearrangements.*

By J. W. COOK, J. JACK, and J. D. LOUDON.

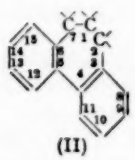
(±)-9 : 12 : 13 : 14-Tetramethoxy-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-dien-2-ol (V) has now been synthesised and is shown to be structurally distinct from the (−)-carbinol formed by the action of nitrous acid on colchinol methyl ether (III). The latter reaction involves Demjanow rearrangement, accompanied by some racemisation, affording (−)- and (±)-9 : 10-dihydro-9-hydroxymethyl-2 : 3 : 4 : 7-tetramethoxyphenanthrene (VI). The (±)-form of this carbinol has also been synthesised and is shown to revert, on dehydration, to the dibenzo*cyclo*heptatriene type of structure.

The interaction of nitrous acid and (±)-9-aminomethyl-9 : 10-dihydro-2 : 3 : 4 : 7-tetramethoxyphenanthrene (VIII) affords, among other products, deaminocolchinol methyl ether (IV) and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene.

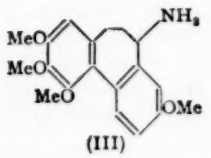
THE structural chemistry of colchicine (I) is complicated by the frequent incidence of molecular rearrangement. This is incurred in the reactions by which ring C becomes benzenoid and is also found at a subsequent stage of degradation wherein contraction of ring B gives rise to derivatives of phenanthrene. Rearrangements of the first type are now recognised as consequences of the tropolone structure present in ring C (for discussion, cf. Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99) : those of the second type appear to reflect a fairly general tendency among derivatives of dibenzo*cyclo*hepta-diene or -triene.



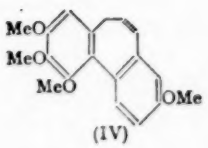
(I)


(II)

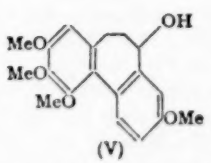
·CH₂·CH:CH· (IIa)
·CO·CH₂·CH₂· (IIb)
·CH₂·CO·CH₂· (IIc)
·CO·CH₂·CH(OH)· (IId)
·CO·CH:CH· (IIe)



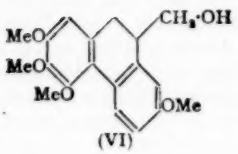
(III)



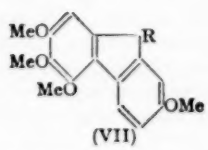
(IV)



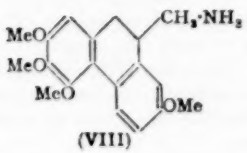
(V)



(VI)



(VII)

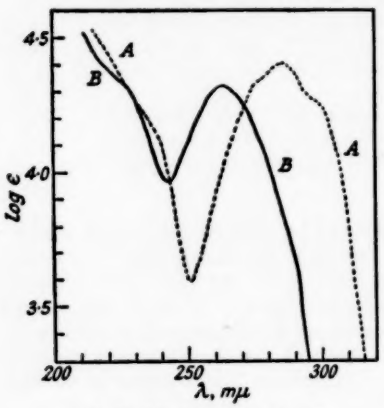


(VIII)

* Part XI, *J.*, 1951, 1397.

The latter tendency is particularly prominent in oxidation reactions and in previous Parts of this series the formation is recorded of appropriate phenanthraquinones from compounds of type (II) comprising the variants (II*a*—*e*) in the three-carbon bridge, with or without methoxyl substituents in the lateral rings [(II*a*), Part V, Barton, Cook, and Loudon, *J.*, **1945**, 176, and Part VI, Cook, Dickson, and Loudon, *J.*, **1947**, 746; (II*b* and *c*), Part VI, *loc. cit.*: (II*d* and *e*), Part XI, Cook, Jack, and Loudon, *J.*, 1951, 1397]. The course of these oxidation reactions is uncertain but phenanthrene-9-carboxylic acids are occasionally found in the products (cf. Part VI, *loc. cit.*) and are probable intermediates. It is noteworthy that 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone could not be detected in comparable oxidations of *N*-acetylcolchinol methyl ether (III; NHAc for NH_2) or similar compounds (cf. Experimental). On the other hand the hydrochloride of an analogous amine (III; H for each OMe) on thermal decomposition affords 9-methylphenanthrene which is also produced by isomerisation from the hydrocarbon (IV; H for each OMe) (Part VI, *loc. cit.*). This last rearrangement explains the conversion of deaminocolchinol methyl ether (IV) into 9-methylphenanthrene by successive treatment with hydriodic acid and distillation from zinc (cf. Parts V and VI, *locc. cit.*).

It was shown in Part I (Cohen, Cook, and Roe, *J.*, 1940, 194) that the action of nitrous acid on colchinol methyl ether yields a mixture of products from which a carbinol, $C_{19}H_{22}O_5$, of m. p. 115·5—116·5° (now designated carbinol-A) was isolated and purified through its *p*-phenylbenzoate. Carbinol-A was lævorotatory (cf. Part V, *loc. cit.*) and was sometimes accompanied by a difficultly separable isomer, carbinol-B (of highest recorded m. p. 157—160°), which we now find to be optically inactive. At that time the structure of colchinol methyl ether was uncertain and formula (VI) was considered for carbinol-A, but was not proved. Dehydration of carbinol-A was later found to yield a mixture of deaminocolchinol methyl ether (IV) and its bond-isomer, *iso*deaminocolchinol methyl ether, of which the structures were unambiguously proved. This dehydration result, when considered together with the now established structure (III) of colchinol methyl ether (Part XI, *loc. cit.*), would suggest formula (V) as the simplest representation of carbinol-A. Such a conclusion, however, would ignore the shift in ultra-violet absorption spectrum in passing from *N*-acetylcolchinol methyl ether to carbinol-A (Part I, *loc. cit.*). Horowitz, Ullyot, Horning, Horning, Koo, Fish, Parker, and Walker (*J. Amer. Chem. Soc.*, 1950, **72**, 4331) pointed out that the absorption spectra of colchinol methyl ether (III) and its *N*-acetyl derivative are not significantly different from that of the parent deaminodihydrocolchinol methyl ether (III; H for NH_2) and it may be inferred that a similarly close relationship would be maintained in the hydroxy-derivative (V). Accordingly, these authors conclude that a central 7-membered ring cannot be present in carbinol-A and, although they do not propose a formula for this compound, they note that its absorption spectrum resembles that of the fluorene derivatives (VII; R = H and $CH_2 \cdot CH_2 \cdot OH$).



A, Carbinol (VI) *in ethanol.*
B, Carbinol (V) *in ethanol.*

In a re-examination of this question the (±)-carbinol (V) was prepared by reduction of the corresponding ketone (Part XI, *loc. cit.*). Its absorption spectrum (see figure) was found to have the expected close relationship to that of *N*-acetylcolchinol methyl ether (III; NHAc for NH_2) (cf. Part I, *loc. cit.*) and to differ from that of (−)-carbinol-A. The latter carbinol, moreover, gave an apple-green solution in concentrated sulphuric acid, whereas (V) dissolved to a red solution. The two carbinols are therefore structurally different.

Since dehydration of (VII; R = $CH_2 \cdot CH_2 \cdot OH$) would be expected to produce the corresponding ethylidenefluorene rather than (IV), attention was next directed to the

carbinol (VI). This (±)-carbinol was prepared by reduction of methyl 9 : 10-dihydro-2 : 3 : 4 : 7-tetramethoxy-9-phenanthroate (cf. Part VII, Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074) with lithium aluminium hydride. Its absorption spectrum (see figure) and colour test with concentrated sulphuric acid were indistinguishable from those of (−)-carbinol-A although the melting points of the two carbinols were distinct. However, in respect of all three criteria carbinol (VI) proved to be identical with (±)-carbinol-B. The conclusion may therefore be drawn that (−)-carbinol-A and (±)-carbinol-B are stereoisomers of structure (VI) and are formed respectively with retention and loss of optical activity through rearrangement from (III) in reaction with nitrous acid. On this basis a further rearrangement, essentially the reverse of the first, must be involved in the dehydration of carbinol-A to a mixture of (IV) and its isomer. Confirmation of this point was accordingly sought by dehydrating carbinol (VI) with phosphoric oxide in boiling xylene. The immediate product was a gum which, in view of the small quantity available, was hydrogenated directly and afforded deaminodihydrocolchinol methyl ether (III; H for NH_2) identical with an authentic sample. These results therefore show that in successive reactions the carbon structure of (III) is rearranged to, and is regenerated from, that of (VI).

The formation of (VI) from (III) is a particular instance of the Demjanow rearrangement, a process which may also be associated with ring-expansion as in the reactions of nitrous acid with certain aminomethyl*cyclo*alkanes (Demjanow, *Chem. Zentr.*, 1903, I, 828; *Ber.*, 1907, **40**, 4961; cf. Nightingale and Maienthal, *J. Amer. Chem. Soc.*, 1950, **72**, 4823). It was therefore of interest to examine the action of nitrous acid on the (±)-amine (VIII) (cf. Part VII, *loc. cit.*). Analogous reactions are known to give rise to complex mixtures of carbinols and olefins (cf. Babier, *Helv. Chim. Acta*, 1940, **23**, 519, 524). In the present case all attempts to isolate a carbinol failed, but the gummy product was separated by chromatography into three crystalline components. Two of these were respectively identified as deaminocolchinol methyl ether (IV) and 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene, of which the former is obviously a product of rearrangement. Analysis of the third compound showed it to be a product of nitration but it was not further investigated.

Finally it may be remarked that the production of deaminocolchinol methyl ether (IV) from (VI), and of its dihydride (III; H for NH_2) from (VIII), constitutes a new synthesis of each of these two degradation products of colchicine. In the light of present experience, however, neither route appears to afford a generally practicable method for the synthesis of dibenz*ocyclo*heptatriene derivatives.

Experimental

Attempted Oxidation of Compounds of Type (III) [With J. MacMillan].—(*a*) A solution of *N*-acetylcolchinol methyl ether (0·2 g.) and sodium dichromate (0·45 g.) in acetic acid (0·6 c.c.) and water (1 c.c.) was heated under reflux for 30 minutes. Neutral material was recovered in chloroform and afforded unchanged *N*-acetylcolchinol methyl ether (0·14 g.) of m. p. and mixed m. p. 202—203° from methanol. There was no evidence of the formation of 2 : 3 : 4 : 7-tetramethoxyphenanthraquinone and the concentrated methanol mother-liquor gave no ketonic product when treated with Girard's reagent T.

(*b*) Under similar conditions 1-acetamido-3 : 4-5 : 6-dibenz*ocyclo*hepta-3 : 5-diene (0·2 g.) was recovered (0·14 g.) without detectable formation of phenanthraquinone.

(*c*) 1-Amino-3 : 4-5 : 6-dibenz*ocyclo*hepta-3 : 5-diene—used as the gummy base from the hydrochloride and alkali—when exposed to similar oxidising conditions was partly recovered as the hydrochloride (0·16 g.) but phenanthraquinone formation was not observed.

(±)-9 : 12 : 13 : 14-*Tetramethoxy*-3 : 4-5 : 6-*dibenzo*cyclo*hepta*-3 : 5-*dien*-2-*ol* (V).—A suspension of lithium aluminium hydride (0·1 g.) in ether was added to a solution of 9 : 12 : 13 : 14-tetramethoxy-3 : 4-5 : 6-dibenz*ocyclo*hepta-3 : 5-dien-2-one (0·05 g.) (Part XI, *loc. cit.*) in the same solvent (10 c.c.). The mixture was heated under reflux for 15 minutes and then cautiously treated with dilute sulphuric acid, and the *alcohol* (V) was recovered from the washed and dried ethereal layer. It formed colourless prisms, m. p. 148—150°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 69·1; H, 6·8. $C_{19}H_{22}O_5$ requires C, 69·05; H, 6·7%) and dissolved in cold concentrated sulphuric acid forming a red solution.

Methyl 9 : 10-*Dihydro*-2 : 3 : 4 : 7-*tetramethoxy*-9-*phenanthroate* was prepared by the action of diazomethane on the corresponding acid (Part VII, *loc. cit.*) and had m. p. 123—124° (from methanol) (Found : C, 66·9; H, 6·4. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%). The *amide* was encountered in course of alkaline hydrolysis of the corresponding nitrile (Part VII, *loc. cit.*) and had m. p. 168° (from methanol) (Found : C, 66·25; H, 5·9; N, 4·3. $C_{19}H_{21}O_5N$ requires C, 66·4; H, 6·2; N, 4·1%).

(±)-9 : 10-*Dihydro*-9-*hydroxymethyl*-2 : 3 : 4 : 7-*tetramethoxyphenanthrene* (VI).—A suspension of lithium aluminium hydride (*ca.* 2 g.) in ether was added to a solution of the above ester (0·75 g.) in ether (30 c.c.). The mixture was heated under reflux for 20 minutes, then cautiously treated with dilute sulphuric acid, and the *carbinol* (VI) was recovered from the washed and dried ethereal layer. It formed colourless rods, m. p. 165—166°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 68·8; H, 6·6. $C_{19}H_{22}O_5$ requires C, 69·05; H, 6·7%) and dissolved in cold concentrated sulphuric acid forming an apple-green solution. The p-*phenylbenzoate* was obtained by heating the carbinol (0·1 g.) with *p*-phenylbenzoyl chloride (0·08 g.) in dry pyridine for 1 hour, and formed colourless plates or needles, m. p. 125—126°, from methanol (Found : C, 75·0; H, 5·7. $C_{32}H_{30}O_6$ requires C, 75·3; H, 5·9%).

The main characteristics of the four carbinols are assembled in the following table :

	Carbinol A	Carbinol B *	Carbinol (VI)	Carbinol (V)
M. p.†	115—116°	157—160°	165—166°	148—150°
M. p. of *p*-phenylbenzoate ...	146—147°	108—109 (cloudy melt)	125	—
Colour with conc. H_2SO_4	Apple-green	Apple-green	Apple-green	Red

* Determined on the very small quantity of B available; $[\alpha]_D^{18}$ in chloroform was zero within experimental limits.

† Mixed m. p. of B and (VI), 164—166°. Mixed m. p. of B and (V), *ca.* 140°.

Dehydration of Carbinol (VI).—Phosphoric oxide (1·5 g.) was added to a solution of the carbinol (0·5 g.) in pure xylene, and the whole was heated under reflux for 15 minutes. The hot xylene solution was decanted and the residue was washed with fresh boiling xylene. The combined xylene solutions were concentrated *in vacuo* affording a gum which was distilled up to 160° (air-bath)/2 × 10^{-4} mm. The gummy distillate was hydrogenated in solution in acetic acid (10 c.c.) over palladised charcoal (0·05 g.). From the filtered solution deaminodihydrocolchinol methyl ether was recovered as a gum which crystallised from methanol as small colourless prisms, m. p. and mixed m. p. 94—96°.

9-*Aminomethyl*-9 : 10-*dihydro*-2 : 3 : 4 : 7-*tetramethoxyphenanthrene* (VIII).—The corresponding 9-cyano-compound was hydrogenated as described in Part VII (*loc. cit.*), and the *amine* (VIII) was recovered in ether from the filtered and basified reaction solution. It formed small colourless prisms, m. p. 138—140° (Found : C, 69·8; H, 7·2; N, 4·5. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·1; N, 4·25%).

Action of Nitrous Acid on Amine (VIII).—A solution of the amine (0·55 g.) in acetic acid (5 c.c.) was treated with a solution of sodium nitrite (1 g.) in water (10 c.c.). The resulting solution was heated at 100° for ½ hour and the dark oil which separated was recovered and washed in ether. Evaporation of the ethereal solution afforded a gum which was distilled at 200—240° (bath-temp.)/0·2 mm. and yielded a brown resinous distillate (0·47 g.). Attempts to form a solid *p*-phenylbenzoate from this distillate were unsuccessful. A solution of the distillate in benzene was passed through a column of alumina. Elution with benzene—controlled by the colour of the bands and their appearance in ultra-violet light—gave four successive fractions yielding respectively (i) an apparently nitrated *substance* obtained as yellow needles, m. p. 115—116°, from methanol (Found : C, 64·0; H, 5·15; N, 3·8. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·4; N, 3·9%), (ii) a yellow uncrystallisable gum, (iii) 2 : 3 : 4 : 7-tetramethoxy-9-methylphenanthrene as colourless prisms, m. p. and mixed m. p. 114—116°, affording the picrate of m. p. and mixed m. p. 145—147°, and (iv) deaminocolchinol methyl ether, m. p. and mixed m. p. 105—110° after repeated crystallisation from methanol.

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111. *The Kinetics of Catalytic Polymerizations. Part I. The Polymerization of Styrene catalyzed by Aluminium Chloride in Carbon Tetrachloride Solution.*

By D. O. Jordan and A. R. Mathieson.

The aluminium-chloride-catalyzed polymerization of styrene in carbon tetrachloride solution has been found to proceed according to a second-order law, the initial rate being proportional to the first power of the concentration of both styrene and aluminium chloride. This law is also obeyed up to high degrees of polymerization, although the values of the velocity constant thus obtained are found to vary with the conditions of the polymerization. The energy of activation calculated from the velocity constants for the initial rate at 0° and 25° is low, being 1200 cal./mole.

From experiments in which the polymerization did not go to completion, it is inferred that one molecule of aluminium chloride initiates, on an average, only one polymer chain. On the addition of further catalyst to an uncompleted reaction, further polymerization occurs. Reactions under very dry conditions proceed at a rate approximately twice that occurring when the drying procedure was less severe; the addition of water and methyl alcohol was found to have little effect on the reaction rate under the latter conditions. It is concluded that the reaction does not require the presence of a co-catalyst.

The polymers obtained are of low molecular weight, being in the range 700—1800. One in every four polymers on an average was found to possess an olefinic double bond. An empirical relation between intrinsic viscosity and molecular weight has been obtained for these polymers of low molecular weight.

The kinetics of the polymerization of certain unsaturated compounds by catalysts of the Friedel–Crafts type have been shown, in the systems so far investigated, to be more complicated than those of the corresponding thermal, photochemical, or peroxide-catalyzed reactions, which can be explained completely by the theory of radical chains. The Friedel–Crafts-catalyzed reactions show a wide divergence of behaviour : the order and mechanism, and the influence of inhibitors and of water and other so-called co-catalysts vary with the nature of the monomer, the catalyst, and the solvent.

The rate of the stannic chloride-catalyzed polymerization of styrene in carbon tetrachloride at ordinary temperatures has been shown by Williams (*J.*, 1940, 775) to be of the first order with respect to the catalyst and of the third order with respect to the monomer. For the same reaction in ethylene dichloride solution, however, Pepper (*Trans. Faraday Soc.*, 1949, **45**, 404) has concluded that the reaction rate is more closely proportional to the second power of the monomer concentration. This result is in agreement with the kinetics of the polymerization of octyl vinyl ether catalyzed by stannic chloride, silver perchlorate, and triphenylmethyl chloride in light petroleum, ethyl ether, and *m*-cresol solutions respectively (Eley and Richards, *ibid.*, p. 436). On the other hand, the titanium tetrachloride-catalyzed polymerization of *iso*butene between −20° and −120° is independent of the catalyst concentration, provided that it is above a certain limit, but is dependent on the concentrations of the co-catalyst and the monomer (Evans, Holden, Plesch, Polanyi, Skinner, and Weinberger, *Nature*, 1946, **157**, 102; Evans, Meadows, and Polanyi, *ibid.*, 1946, **158**, 94; Plesch, Polanyi, and Skinner, *J.*, 1947, 257; Plesch, *Research*, 1949, **2**, 267), the exact kinetic relationships not being known. A similar result has been reported by Norrish and Russell (*Nature*, 1947, **160**, 543) for the polymerization of *iso*butene in ethyl chloride solution catalyzed by stannic chloride.

The widest divergence between the various reactions appears to exist in the necessity, or otherwise, for the presence of traces of water. The presence of water has been shown to be essential for the polymerization of *iso*butene at low temperatures catalyzed by stannic chloride (Norrish and Russell, *loc. cit.*), and by titanium tetrachloride (Plesch, Polanyi,

and Skinner, *loc. cit.*), which are both relatively weak Friedel–Crafts catalysts. The more active boron trifluoride catalyzes the polymerization of *iso*butene in the absence of water in the liquid phase at low temperatures, but not in the gas phase (Evans, Meadows, and Polanyi, *Nature*, **1947**, **160**, 867). The early work of Williams (*J.*, 1938, 246, 1046; 1940, 775) and of Eley and Pepper (*Trans. Faraday Soc.*, 1947, **43**, 112) cannot be discussed in this connection since at that time the possibility that water might be a co-catalyst was not realised. However, the results of Williams (*loc. cit.*) have been re-examined by Plesch (*loc. cit.*), who has argued that it would appear that water accelerates the catalysis of styrene by stannic chloride and does not retard it as originally suggested by Williams. Eley and Richards (*loc. cit.*) also find that the silver perchlorate-catalyzed polymerization of octyl vinyl ether is accelerated by the addition of water, but it must be clearly pointed out that there is a marked difference between the action of water in these reactions, where the presence of water accelerates the reaction but is not an essential co-catalyst, and the low-temperature polymerization of *iso*butene described above, where the reaction does not take place at a measurable rate except in the presence of water in addition to the Friedel–Crafts catalyst. In marked contrast to both these types of behaviour, Eley and Richards (*loc. cit.*) have found that the stannic chloride-catalyzed polymerization of octyl vinyl ether was unaffected by the addition of water, and Pepper (*Trans. Faraday Soc.*, 1949, **45**, 397) has observed that the effect of careful drying of the reactants and solvent is to *increase* the rate of polymerization of styrene catalyzed by stannic chloride in ethylene dichloride and nitrobenzene solutions. For the same reaction in a mixture of carbon tetrachloride and nitrobenzene as solvent, George and Wechsler (*J. Polymer Sci.*, 1951, **6**, 725) found that addition of small amounts of water had no effect and that the presence of large amounts of water markedly decreased the reaction rate.

In view of these differences in behaviour it is evident that before a detailed interpretation of the data in terms of general reaction mechanisms can be made, other catalyzed polymerizations must be studied. In the present work, which has been briefly reported elsewhere (Jordan and Mathieson, *Nature*, 1951, **161**, 523), aluminium chloride has been employed as the catalyst for the polymerization of styrene, partly in order that comparison could be made with the results of Williams and of Pepper (*locc. cit.*), but also because the reaction proceeds at a rate convenient for kinetic study.

Results

Quantitative Character of the Polymerization.—Any analysis of the kinetic data must necessarily involve the assumption that consumption of monomer in side reactions is negligible. The results given in Table I show that this is so in the reaction under consideration, the weight of polystyrene recovered being the same, within the limits of experimental error, as the weight of monostyrene consumed.

Table 1. *The quantitative character of the polymerization.*

Initial concn. of monomer (mole/l.)	Temp.	Monomer consumed (%)	Monomer consumed in arbitrary volume of solution (g.)	Polymer recovered from same volume (g.)
0·523	0°	80·9	0·950	0·946
0·657	0	83·7	1·372	1·368
0·272	25	89·9	0·482	0·412
0·141	25	86·0	0·120	0·129
0·219	25	73·5	0·129	0·131
0·277	25	43·7	0·264	0·260
0·380	25	56·0	0·440	0·464
0·320	35	54·2	0·400	0·399

The Time Course of the Polymerization.—Typical curves showing the course of the reaction at 25° and 0° are given in Figs. 1 and 2. The results show that the method of analysis of the reaction mixture adopted leads to an excellent definition of the shape of the curves such as is essential for kinetic analysis. In Fig. 1 one reaction shows a short induction period. Only three such reactions have been observed in the twenty-seven experiments performed in which the initial concentrations of monomer and catalyst have been varied. It is evident that a period

FIG. 1. *The course of polymerization at 25° (typical curves).*

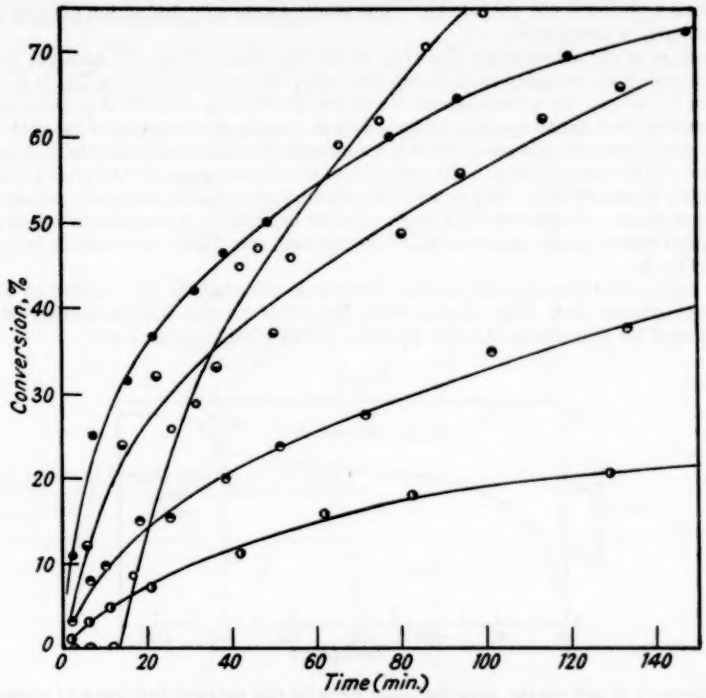
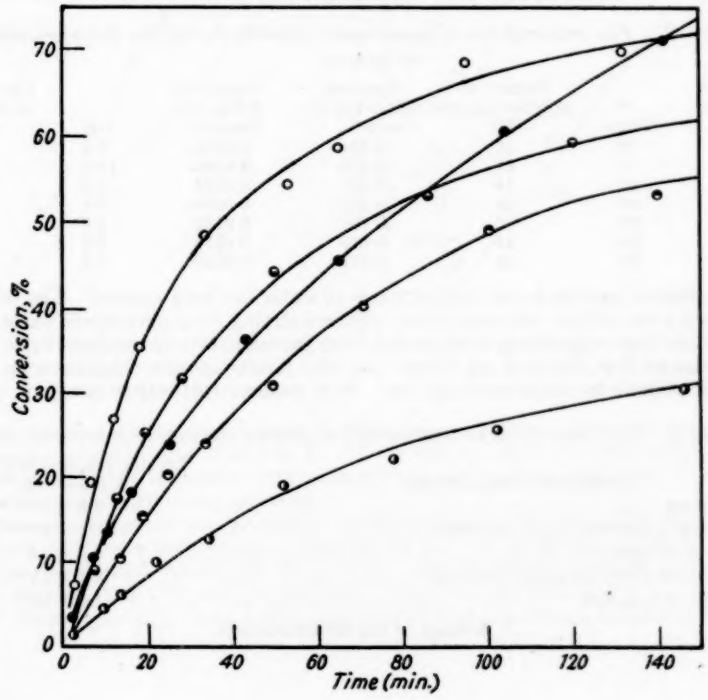


FIG. 2. *The course of polymerization at 0° (typical curves).*

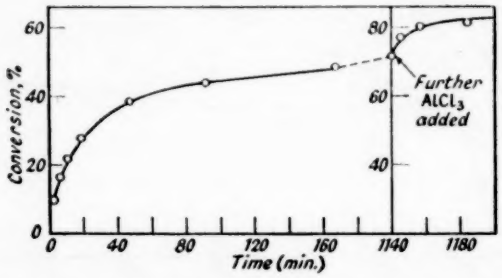


of induction is not a general feature of this reaction, and the reason for an occasional reaction possessing such a period is not yet known. The reactions showing induction periods have therefore not been further considered.

The Function of the Aluminium Chloride in the Reaction.—That the catalyst is consumed during the course of the reaction may be inferred from the results shown in Table 2. First, the reaction does not always go to completion when the aluminium chloride is present in relatively low concentration, and, secondly, the values given in column 6 of Table 2 of the ratio of styrene polymerized to aluminium chloride present is a constant for those reactions which do not proceed to completion. The value of this ratio approximates to the value of the chain length of the polymer, which indicates that, on average, one aluminium chloride molecule initiates only one polymerization chain. Furthermore, if fresh catalyst is added to a reaction in which polymerization has ceased before all the monomer has polymerized, it is found that further polymerization takes place (Fig. 3).

Another instance of the consumption of catalyst is afforded by the results of Hersberger, Reid, and Heiligmann (*Ind. Eng. Chem.*, 1945, **37**, 1073) for the polymerization of α-methylstryene catalyzed by aluminium chloride in ethyl chloride solution at −50°.

FIG. 3.



The Influence of Water on the Reaction.—In view of the marked influence of water that has been observed in some other systems (Norrish and Russell, *loc. cit.*; Plesch, Polanyi, and Skinner,

TABLE 2. *The consumption of aluminium Chloride during the polymerization of styrene.*

Initial concn. of monomer (mole/l.)	Temp.	Extent of polymerization (%)	Monomer consumed (x) (mole/l.)	Concn. of $AlCl_3$ (B) (mole/l.)	x/B	Chain length in monomer units
0·505	0°	46	0·234	0·0326	7·2	7·3
0·559	0	67	0·374	0·0250	15·0	—
0·277	25	44	0·121	0·0176	6·9	10·5
0·380	25	56	0·213	0·0300	7·1	7·1
0·279	25	36	0·101	0·0182	5·5	5·3
0·498	25	34	0·170	0·0233	7·3	—
0·320	35	54	0·174	0·0240	7·1	8·7

loc. cit.) the effect of careful drying and of traces of water has been studied. The solvent was normally dried over calcium chloride; more vigorous drying over phosphoric oxide, and the complete exclusion of atmospheric moisture led to an increased rate of reaction (Table 3). This result is similar to that obtained by Pepper (*loc. cit.*) for the stannic chloride-catalyzed polymerization of styrene in ethylene dichloride. It is evident that water does not behave as

TABLE 3. *Influence of water and methyl alcohol on the rate of polymerization.*

Conditions of experiments	Specific reaction rate at 25°, l. mole^{-1} sec.$^{-1}$
Rigorous drying	$3·3 \times 10^{-2}$
Dried with $CaCl_2$ (normal exptl. conditions)	$1·68 \times 10^{-1}$ *
0·0035 mole/l. of water	$1·5 \times 10^{-1}$
0·0075 mole/l. of water (saturated solution)	$1·8 \times 10^{-1}$
0·0388 mole/l. of CH_3·OH	$1·8 \times 10^{-1}$

* Average of ten determinations.

a co-catalyst, but very small concentrations of water and perhaps methyl alcohol are clearly capable of producing a small decrease in the rate, the rate becoming constant at a very low and as yet undetermined concentration of water.

It is conceivable that traces of other substances present in the carbon tetrachloride or the styrene might act as co-catalysts. Co-catalysts have been shown to be consumed during the course of reaction (see Plesch, *loc. cit.*), and hence the further addition of catalyst only to an

FIG. 4.—*The relation between* $[\eta]$ *and molecular weight.*

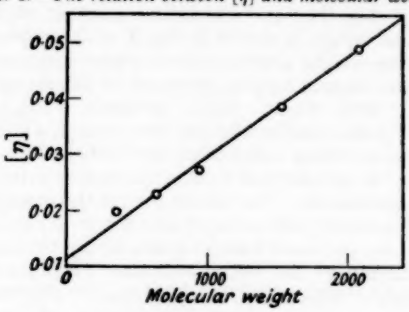
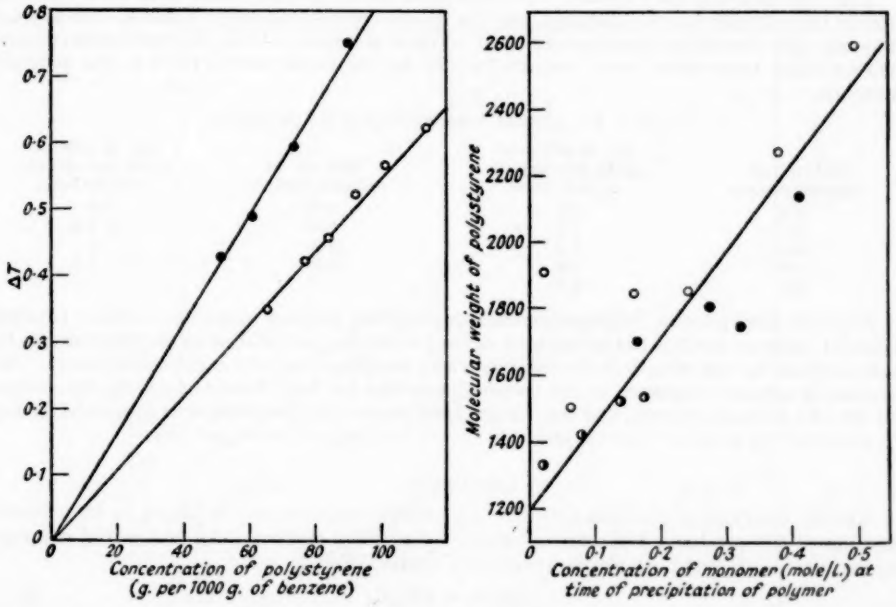


FIG. 5. *Variation of freezing-point depression with concentration of polystyrene (molecular weights :* ● 630; ○ 930).

FIG. 6.



incomplete reaction should not promote further polymerization. That this does not obtain in the present system is clear from Fig. 3; it may also be concluded that co-catalysts do not exist either in the carbon tetrachloride or in the styrene, although the possibility of their existence in the aluminium chloride is not excluded.

The Molecular Weight of the Polystyrene.—Various empirical formulæ of the type $[\eta] = A + BM$ or $[\eta] = BM^a$ have been proposed relating the polymer molecular weight to the intrinsic viscosity (see Kemp and Peters, *Ind. Eng. Chem.*, 1942, **34**, 1097; Bamford and Dewar, *Proc. Roy. Soc.*, *A*, 1948, **192**, 329) and the formula of Bamford and Dewar (*loc. cit.*), $[\eta] = 4{\cdot}40 \times 10^{-4}M^{0{\cdot}65}$ where $[\eta] = \eta_{sp}/c$ and c is the concentration in g. per 100 c.c. of solution, in particular

has been frequently used.* However, the molecular weights of the polystyrenes isolated in the present study are low and fall outside the range of molecular weights on which the Bamford and Dewar formula was based; furthermore, owing to the low values of the molecular weights of our polystyrenes direct comparison with the molecular weight determined cryoscopically is possible. We have therefore obtained the empirical formula

$$[\eta] = 0{\cdot}0115 + 1{\cdot}81 \times 10^{-5}M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(where $[\eta]$ is defined as above) by determining the intrinsic viscosity and the cryoscopic molecular weights in benzene solution (Fig. 4). That the cryoscopic method gives a true value for the number average molecular weight is shown in Fig. 5, which shows clearly that Raoult's law holds for these low-molecular-weight polymers in benzene solution. The empirical relation (1) may be compared with the original formula proposed by Staudinger (" Die Hochmolecularen organischen Verbindungen," 1932, Berlin, Julius Springer), $[\eta] = 1{\cdot}8 \times 10^{-5}M$. The results of Kemp and Peters (*loc. cit.*) yield a similar relation, but, without a knowledge of the temperature of their viscosity measurements, direct comparison is of little value.

The molecular weight of the polystyrene formed decreases during polymerization as shown in Fig. 6 for three typical experiments. The results for the three polymerizations having different initial concentrations of monomer and catalyst are seen to lie on the same straight line.

The molecular weight of the polymers formed generally lay between 700 and 1800, the variation showing some dependence on the initial monomer concentration as found by Pepper (*loc. cit.*) but not on the catalyst concentration. This is to be expected from the results shown in Fig. 6 and is in agreement with the results of Williams (*loc. cit.*) and Pepper (*loc. cit.*). Over the small temperature range studied little variation of molecular weight with temperature was observed.

The Constitution of the Polymer.—Estimations of olefinic double bonds have been made on some of the polymer samples prepared, and the results are summarized in Table 4. On average there was only one double bond in every four polymer molecules, so that any mechanism postulated for chain termination must account for only an occasional double bond in the polymer molecules.

TABLE 4. *Double bond content of the polymers.*

Mol. wt. of polymer sample	No. of polymer mols. per olefinic double bond	Mol. wt. of polymer sample	No. of polymer mols. per olefinic double bond
350	8·7	900	1·0
580	1·0	930	7·3, 5·8
630	4·3	1100	1·1
740	9·6	1520	3·9, 4·1
760	2·6		

It has not been possible to determine whether or not the polymer molecules contain a catalyst fragment, since no method has as yet been devised whereby precipitation of the polymer can be made without the use of hydroxylic solvents which would remove any catalyst fragment. The presence of catalyst fragments in the polymer molecules has been demonstrated by Staudinger (*loc. cit.*) for a similar system, and since it has been shown that the catalyst is consumed during the course of the reaction it seems probable that it is combined in the polymer.

DISCUSSION

Kinetic Analysis of the Rate Curves.—The initial reaction rate is found to be a linear function of the product of the first powers of the initial styrene (M_0) and initial catalyst concentrations (B_0) at both the temperatures studied (Fig. 7), *viz.*:

$$-\mathrm{d}M/\mathrm{d}t = kM_0B_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The agreement between this relation and the experimental results is such as to exclude completely the law

$$-\mathrm{d}M/\mathrm{d}t = kM_0^2B_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

* In Table III (p. 334) in the paper of Bamford and Dewar (*loc. cit.*), it has been erroneously assumed that the values of $(\log \eta)/c$ given by Kemp and Peters (*loc. cit.*, table III, p. 1099) were equivalent to $[\eta]$; this is not so since the logarithms used by Kemp and Peters are to the base 10. The values of the molecular weight calculated by Bamford and Dewar from Kemp and Peters's viscosity data are therefore too low by a factor of $2{\cdot}303^{1/0{\cdot}65} = 3{\cdot}63$ and therefore do not agree with the cryoscopic molecular weights given by Kemp and Peters. It would thus appear that Bamford and Dewar's formula is not generally applicable to polystyrenes of low molecular weight.

FIG. 7. *The concentration dependence of the initial rate of polymerization* (○ *at* 25°; ● *at* 0°).

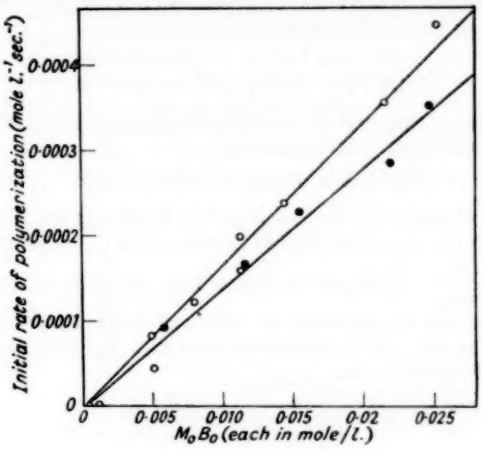
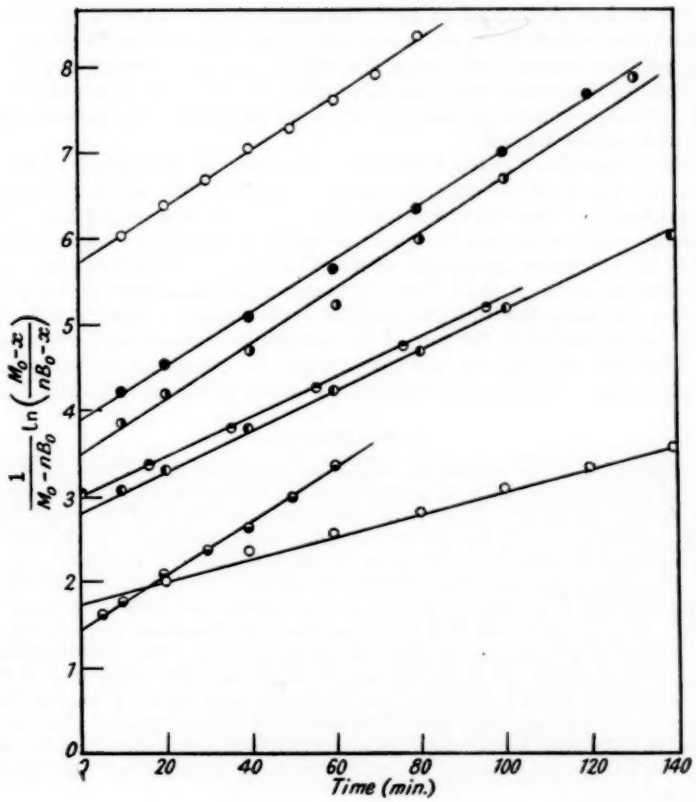


FIG. 8.



observed by Eley and Richards (*loc. cit.*) for the polymerization of octyl vinyl ether catalyzed by stannic chloride, silver perchlorate, and triphenylmethyl chloride, and by Pepper (*loc. cit.*) for the stannic chloride-catalyzed polymerization of styrene. From Fig. 7 the following values of the overall velocity constant are obtained :

$$\text{at } 0°,\ k = 1{\cdot}40 \times 10^{-2} \text{ l. mole}^{-1} \text{ sec.}^{-1}$$
$$\text{at } 25°,\ k = 1{\cdot}68 \times 10^{-2} \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

The validity of the kinetic equation (2) is confirmed by an analysis of the rate curves up to high degrees of polymerization. The equation,

$$-\mathrm{d}M/\mathrm{d}t = k'(M_0 - x)^p(B_0 - x/n) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where x is the amount of monomer consumed in time t, and n is the chain length in monomer units, was found to fit the rate curves always when $p = 1$. This is illustrated in Fig. 8, where $\frac{1}{M_0 - nB_0} \cdot \ln \frac{(M_0 - x)}{(nB_0 - x)}$ is plotted against time, for some typical experiments. When $p = 2$ or 3 the equation did not generally fit, although in a few instances owing to the form of the integrated expressions all the equations gave equally good agreement. The values of k' in the integrated form of (4), *viz.*,

$$k' = \frac{1}{t} \cdot \frac{n}{M_0 - nB_0} \cdot \ln \frac{nB_0(M_0 - x)}{M_0(nB_0 - x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

were obtained by plotting $[1/(M_0 - nB_0)] \ln [(M_0 - x)/(nB_0 - x)$ against t, the slope of the straight lines then giving k'/n (see Fig. 8). The values of k' so obtained varied from one experiment to another within the range $0{\cdot}15 \times 10^{-2}$ to $0{\cdot}94 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$. These values are lower than that obtained from the initial slope. This variation in k' is to be expected since the method is not to be regarded as accurate for the evaluation of velocity constants in polymer kinetics (see Pepper, *loc. cit.*) in view of the complexity of the reaction, and also because of the sensitivity of the value of k' (but not of k) to the factor $(M_0 - nB_0)$ occurring in the denominator of equation (5), since nB_0 frequently approaches M_0 in the later stages of a polymerization.

Temperature Dependence of the Reactions.—The value of the energy of activation calculated from the values of the velocity constant obtained from the initial rates at 0° and 25° is 1200 cal./mole. This very low value is less than that obtained by Eley and Richards (*loc. cit.*) for the polymerization of octyl vinyl ether catalyzed by stannic chloride (10,000 cal./mole) but in reasonable agreement with the statement of Williams (*loc. cit.*) that the energy of activation for the stannic chloride-catalyzed polymerization of styrene is less than 3000 cal./mole. As pointed out by Eley and Richards (*Research*, 1949, **2**, 147; *loc. cit.*) the overall energy of activation is the sum of the energies of activation of several intermediate stages (*e.g.*, initiation, propagation, and termination), the energies of activation for which are not necessarily so low. The overall energy of activation is then given by $E = E_i + E_p - E_t$.

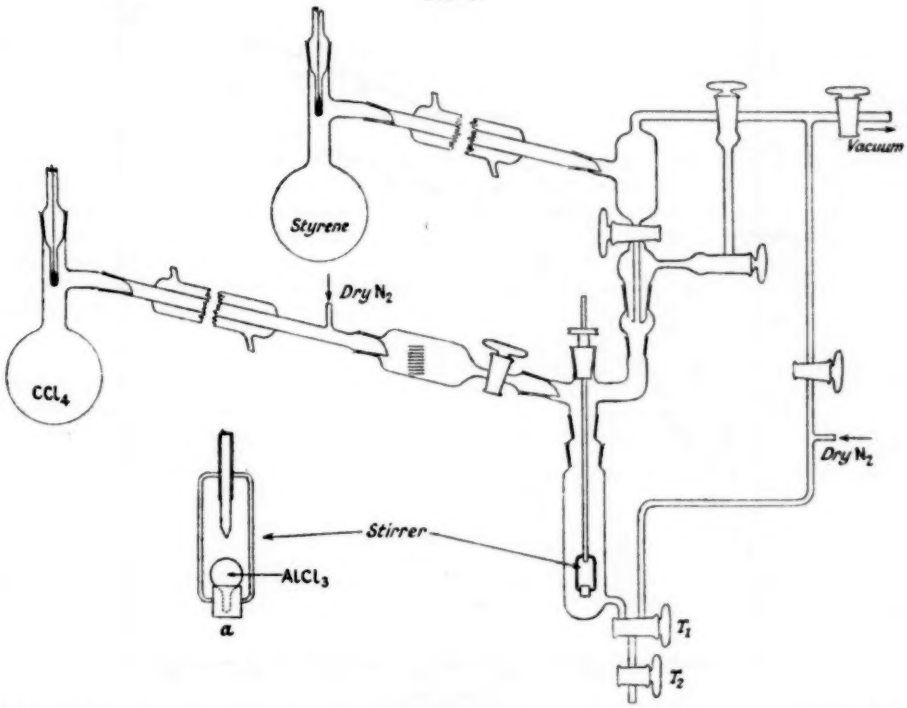
Experimental

Reaction Apparatus.—The apparatus, which was constructed of Pyrex glass, is shown in Fig. 9. It consists essentially of three isolatable parts, the reaction vessel, and the styrene and the carbon tetrachloride stills. Each section was evacuated and filled twice with dry nitrogen. The stirrer in the reaction vessel was not high-vacuum tight, although it could hold low vacua. It was made high-vacuum tight by being sealed on the outside with " Apiezon " ' Q ' compound, which was subsequently removed when stirring was begun. During the reaction the vessel was filled with dry nitrogen at a pressure slightly above atmospheric further to ensure that no air could leak in. The catalyst was originally contained in evacuated glass bulbs which were placed in the saddle of the specially constructed stirrer (Fig. 9*a*). The bulb could be shattered at a specified time by means of the copper ramrod which was then lifted clear of the solution. The ramrod, which slid in the stirrer tube, was lubricated with silicone grease and was vacuum tight. All ground joints and taps were lubricated with silicone grease. The withdrawal of samples of known volume of the reaction mixture was made without influencing the dry character of the reaction by manipulation of taps T_1 and T_2. Solvent and monomer were distilled directly into the reaction vessel.

Normally, reactions were carried out in a simplified apparatus which resembled the reaction vessel in Fig. 9 but the solvent and monomer, although dry and redistilled, were not distilled straight into the vessel. The weight of aluminium chloride employed in the reactions was determined by weighing the bulb containing it before the experiment, and isolating and weighing the glass residue at the end of the experiment.

Determination of Styrene.—Samples of the reaction mixture were withdrawn and added to excess of a standard solution of bromine in glacial acetic acid. The excess of bromine was immediately destroyed by the addition of potassium iodide, and the liberated iodine titrated with standard sodium thiosulphate. It has been shown by Williams (*loc. cit.*) that this method accurately determines only the monostyrene present so long as the excess of bromine is quickly removed.

FIG. 9.



Temperature Control.—Reactions at 25° and 35° were carried out in a water-thermostat, with an accuracy of ± 0·05°. Reactions at 0° were carried out in melting ice in a vacuum-flask.

Reproducibility of Reaction Rate.—The satisfactory nature of the procedure outlined is demonstrated in Fig. 10 where the degree of polymerization is plotted against time for two sets of two experiments having the same initial value of M_0B_0. Excellent agreement is obtained up to 40% polymerization, and even beyond this value the scatter of points is quite small.

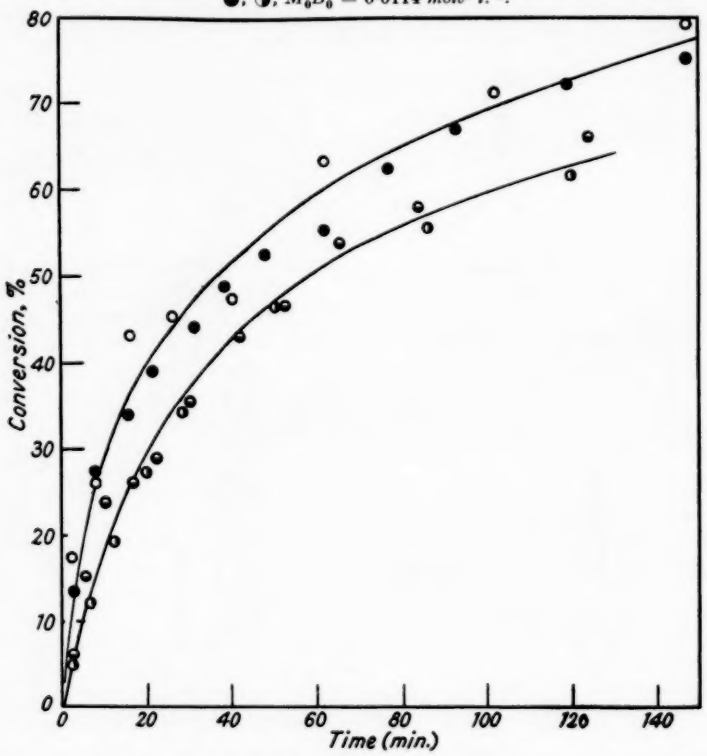
Precipitation of the Polymer.—Two methods have been used for the isolation of the polymer from the reaction mixture, and both yielded identical polymers, as shown by cryoscopic and viscosity determinations from the same reaction mixture. The methods adopted were (1) precipitation with methyl alcohol followed by evaporation of the whole mixture to dryness at room temperature, washing of the solid residue with methyl alcohol to remove styrene and aluminium chloride, and finally drying with slight warming, and (2) as in (1) but with the first step omitted. The necessity of evaporating the whole of the reaction mixture instead of collecting the precipitated polymer is due to the non-precipitation of the fraction of low molecular weight by the methyl alcohol. Once obtained in the semi-solid state, however, these fractions of low molecular weight did not redissolve in the methyl alcohol washings. Method (1) was

always employed when it was necessary to stop the reaction at a particular time. Table 1 indicates that these procedures were effective in recovering all the polymer.

Viscosity.—This was measured in an Ostwald viscometer in a thermostat at 25° ± 0·05°. The polymer was dissolved in benzene, and the solution freed from dust by passage through a sintered-glass filter. Below a polymer concentration of 6 g./100 c.c., η_{sp}/c was constant, but this was always verified by determining η_{sp} at least at two concentrations.

Cryoscopic Measurements.—Molecular weights of the polymers were determined in benzene solution by the Beckmann freezing-point method. Solid solutions were not formed since the solid separating was shown to be pure benzene.

FIG. 10. *Reproducibility of polymerization.* ○, ●, $M_0B_0 = 0{\cdot}0250$ *mole*^{2} *l.*$^{-2}$; ◒, ◑, $M_0B_0 = 0{\cdot}0114$ *mole*^{2} *l.*$^{-2}$.



Determination of Olefinic Double Bonds in the Polymers.—This was made by treating the polymer in carbon tetrachloride in a greased-stoppered bottle with a solution of bromine in glacial acetic acid for several hours; the unchanged bromine was determined as previously described. Blank determinations were always made.

Materials.—Styrene, obtained from Messrs. Lights Ltd., was kept in amber-coloured bottles in the presence of a quinone inhibitor. It was given at least three vacuum-distillations immediately before use. In experiments carried out under rigorously dry conditions eight such distillations were given. Aluminium chloride, obtained from the British Drug Houses Ltd., was sublimed once in air, and then eight successive times in a vacuum in an enclosed system. The specimens were kept in evacuated glass bulbs. Carbon tetrachloride was redistilled from calcium chloride immediately before use; where careful drying was necessary, phosphoric oxide was used. Benzene, of AnalaR quality, was redistilled and kept over sodium.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 10th*, 1951.]

112. *The Kinetics of Catalytic Polymerizations. Part II.* The Mechanism of the Polymerization of Styrene catalyzed by Aluminium Chloride.*

By D. O. Jordan and A. R. Mathieson.

The kinetics of the individual stages of the aluminium chloride-catalyzed polymerization of styrene are considered on the basis of the experimental results given in Part I (preceding paper). Tentative conclusions are drawn concerning the mechanism of the reaction and in particular concerning the part played by the aluminium chloride in the reaction.

In Part I * it has been shown that the initial rate of the polymerization of styrene in carbon tetrachloride solution catalyzed by aluminium chloride may be represented by the law

$$-\mathrm{d}M/\mathrm{d}t = kM_0B_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where M_0 and B_0 are the initial concentrations of styrene and aluminium chloride respectively. From this equation a reaction scheme may be built up taking into consideration the following possible initiation, propagation, chain-transfer, and chain-termination reactions (see, *e.g.*, Hulbert, Harman, Tobolsky, and Eyring, *Ann. New York Acad. Sci.*, 1943, **44**, 371).

Initiation.—This must take place by collisions of molecules of monomer (m) and of catalyst (b) :

$$\mathrm{m} + \mathrm{b} \longrightarrow \mathrm{m_1}^* \quad V_i = k_iMB \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In view of the fact that the course of the reaction is not influenced by co-catalysts, this becomes the only possible initiation reaction.

Propagation.—It is generally assumed that this occurs by the reaction

$$\mathrm{m_1}^* + \mathrm{m} \longrightarrow \mathrm{m_2}^* \quad V_p = k_pGM \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

or, in general,

$$\mathrm{m_n}^* + \mathrm{m} \longrightarrow \mathrm{m_{n+1}}^*$$

where G is the concentration of the growing polymer chains.

Termination.—The only reaction compatible with (1) is of the type termed monomer deactivation :

$$\mathrm{m_n}^* + \mathrm{m} \longrightarrow \mathrm{m_{n+1}} \quad V_t = k_t\mathrm{GM} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

This termination reaction has been suggested previously by Schultz (*Z. physikal. Chem.*, 1935, *B*, **30**, 379) for the thermal polymerization of styrene, but differs from that suggested by Eley and Pepper (*Trans. Faraday Soc.*, 1947, **43**, 112), Pepper (*ibid.*, 1949, **45**, 404), and Eley and Richards (*ibid.*, p. 436) for similar systems, who found that the reaction

$$\mathrm{m_n}^* \longrightarrow \mathrm{m_n} + \mathrm{b} \quad V_t' = k_t'G \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

was necessary to satisfy their rate equation

$$-\mathrm{d}M/\mathrm{d}t = kM_0{}^2B_0$$

The monomer deactivation form of termination, (4), is in agreement however, with George and Wechsler's conclusion (*J. Polymer Sci.*, 1951, **6**, 725) that the termination reaction in the stannic chloride-catalyzed polymerization of styrene cannot be unimolecular. Furthermore, the unimolecular process, (5), would probably bring about the re-formation of active catalyst, which is contrary to our findings (see Part I).

* Part I, preceding paper.

Other possible termination reactions which have been shown to occur in free-radical polymerizations are :

$$\text{recombination} \quad m_n^* + m_m^* \longrightarrow m_{n+m}$$

$$\text{disproportionation} \quad m_n^* + m_m^* \longrightarrow m_n + m_m$$

These termination reactions have not been found to satisfy the conditions of the catalyzed reactions of the type considered here.

Transfer Reactions.—Solvent- and monomer-transfer reactions are the only transfer reactions which need be considered for the initial mechanism. These are :

$$m_n^* + m \longrightarrow m_n + m^* \quad V_{tr} = k_{tr}GM \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$m_n^* + s \longrightarrow m_n + s^* \quad V_{st} = k_{st}GS \quad . \quad . \quad . \quad . \quad . \quad (7)$$

possibly followed by

$$s^* + m \longrightarrow m^* + s \quad V_s = k_sS^*M \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where S and S^* are the concentrations of solvent and activated solvent molecules respectively.

Reactions involving deactivated polymer chains are unlikely to influence the kinetics of the initial reaction, but it must be borne in mind that conclusions derived from reactions proceeding to a high degree of polymerization may be influenced, in the later stages, by such reactions. This applies in particular to observations based on the molecular weight of the polymers formed.

The observation that one catalyst molecule initiates only one polymer chain on average (see Part I, Table 2) indicates that transfer reactions are of little importance in determining the mechanism of this particular polymerization, in contrast to Eley and Richards's conclusions (*Research*, 1949, **2**, 147 ; and *loc. cit.*). It therefore follows (see Mayo, *J. Amer. Chem. Soc.*, 1945, **65**, 2324 ; Breitenbach and Maschin, *Z. physikal. Chem.*, 1940, *A*, **187**, 175) that if the solvent participates in the reaction it does so by a true termination reaction, of the type given by (7) above.

The Kinetic Equation.—The assumption of the steady-state criterion,

$$dG/dt = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

and hence that

$$V_i = V_t + V_{st} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

appears to be justified in this reaction. From equations (2), (4), (7), and (9), the concentration (G) of growing polymer chains may be calculated :

$$G = k_iMB/(k_tM + k_{st}S) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The total rate of monomer consumption is given by :

$$-dM/dt = V_i + V_p + V_t + V_{tr} + V_s$$

in which we may with justification neglect V_{tr} and V_s.

Hence

$$-dM/dt = k_iMB[1 + M(k_p + k_t)/(k_tM + k_{st}S)] \quad . \quad . \quad . \quad (12)$$

This is only in agreement with the experimental equation (1) if V_{st} is small compared with V_t, in which case equation (12) reduces to :

$$-dM/dt = k_iMB[2 + k_p/k_t] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

The decrease in molecular weight observed during the reaction (see Part I, Fig. 6) may be regarded as evidence for the operation of the solvent termination reaction (7), since the concentration of solvent must increase during the reaction, *i.e.*, the volume of the system decreases (see Pepper, *loc. cit.*). The chain length (n) in monomer units is then given by :

$$n = V_p/(V_t + V_{st}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14a)$$

whence

$$1/n = k_t/k_p + k_{st}S/k_pM \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14b)$$

The linearity of the plot of molecular weight against monomer concentration at time of precipitation (Part I, Fig. 6) is of no special significance, since the polymer precipitated is

the whole mass of polymer formed up to that time. A more valid correspondence should be obtained between the molecular weight of the polymer precipitated and the monomer concentration when half the amount of reaction up to that time has occurred [*i.e.*, $\frac{1}{2}(M_0 + M)$]. The plot of molecular weight against $\frac{1}{2}(M_0 + M)$ is shown in Fig. 1 and is not found to be linear. From equation (14), however, we should expect that the plot of $1/n$ against $S/\frac{1}{2}(M_0 + M)$ should be linear and that this is the case is shown in Fig. 2.

FIG. 1.

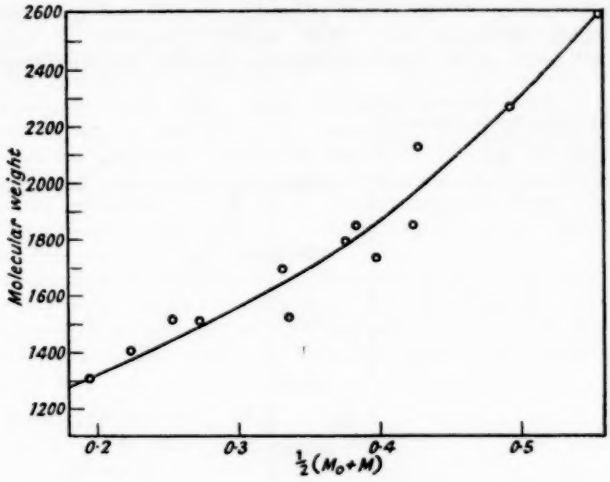
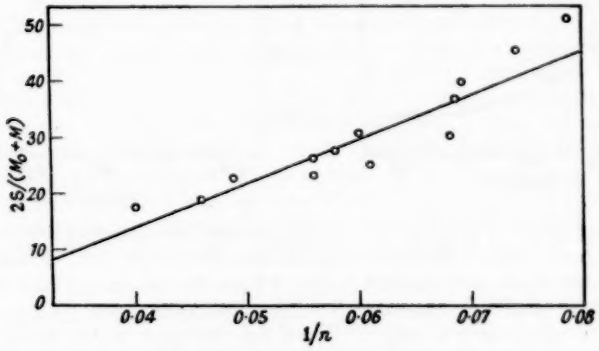


FIG. 2.



Calculation of Individual Reaction Constants.—From the slope of the line in Fig. 2 we may obtain the ratio k_{st}/k_p for which the value 0·0014 is found. The solvent termination reaction is thus clearly not responsible for the low molecular weight of the polymers formed and this can be attributed to the termination reaction (4). This fact, together with the unimportance of transfer reactions, enables us to write in place of (14*a*)

$$n \approx V_p/V_t$$

Since the average value of n is approximately 7 at 25°,

$$1/n = 0{\cdot}14 \approx k_t/k_p$$

Thus $k_t \approx 100k_{st}$, and this fact justifies to some extent the neglect of V_{st} in equation (12) for the range of initial concentrations studied, but indicates also that this value of k_{st}, derived as it is by a consideration of large amounts of reaction, is probably too high.

Putting the constant term of equation (13) equal to the experimental overall constant k of equation (1) we obtain

$$k = k_i(2 + k_p/k_t)$$

and, inserting the value of k_p/k_t (at 25° $k_p/k_t = 7$ and at 0° $k_p/k_t = 11$), we may calculate k_i at 0°, $k_i = 1{\cdot}1 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$, and, at 25°, $k_i = 1{\cdot}9 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. Unfortunately these values cannot as yet be checked experimentally as no suitable inhibitor has been found for this reaction. Nevertheless, these values are of the order expected from a knowledge of the slower polymerization caused by stannic chloride as catalyst, for which Williams (*J.*, 1938, 1045) calculated a value of k_i of $1{\cdot}7 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25° from a measurement of the inhibiting effect of hydrogen chloride on the reaction. The value of k_i at 25° for the corresponding free-radical reaction is $1{\cdot}32 \times 10^{-16}$ l. mole^{-1} sec.$^{-1}$ (Bamford and Dewar, *Proc. Roy. Soc.*, *A*, 1948, **192**, 309).

FIG. 3. *Variation of* $[\eta]$ *with temperature of preparation for poly-α-methyl styrene* (○) *(results of Hersberger, Reid, and Heiligmann) and polystyrene* (●).

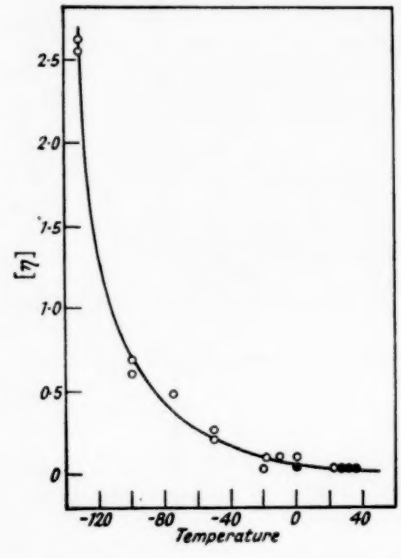
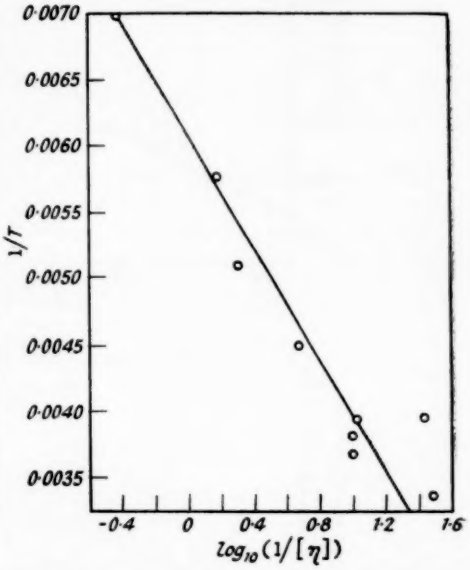


FIG. 4.



The extrapolation of the straight line in Fig. 2 from the values in dilute solution to give k_t/k_p is not justifiable (Hulburt, Harman, Tobolsky, and Eyring, *loc. cit.*).

Estimation of the Activation Energies.—From the variation of the molecular weight of the polymers with temperature of preparation it is possible to calculate $E_p - E_t - E_{st}$ (where E_p, E_t, and E_{st} are respectively the energies of activation for the propagation, termination, and solvent termination reactions). Introducing activation energies into equation (14*b*) and taking logarithms, we obtain :

$$\log \frac{1}{[\eta]} \propto \log \frac{1}{n} = \text{const.} + \frac{E_p - E_t - E_{st}}{RT} + \log \frac{S}{M} \quad . \quad . \quad . \quad (15)$$

We may regard S/M as a constant if the reactions have the same initial monomer concentration. It then follows that a plot of log $(1/[\eta])$ against $1/T$ should give a straight line of slope $(E_p - E_t - E_{st})/R$.

The variation of the polymer molecular weight with temperature for the aluminium chloride-catalyzed polymerization of styrene over the range 0° to 35° was too small to test this equation. However, Hersberger, Reid, and Heiligmann (*Ind. Eng. Chem.*, 1945, **37**,

1073) have investigated the variation of molecular weight with temperature over the range −130° to 23° of poly-α-methylstyrene, prepared with aluminium chloride as catalyst in ethyl chloride solution. At temperatures higher than −20° they also find only a small variation of molecular weight with temperature. Below this temperature, however, the molecular weight increases considerably as the temperature is lowered. Both sets of results are shown in Fig. 3, in which $[\eta]$ is plotted as a function of T. The two sets of results fall on the same curve where the temperatures are comparable. These data are applied to equation (15) in Fig. 4 which shows the required linear relation; from the slope, a value of −3800 cal./mole is obtained for $E_p - E_t - E_{st}$ on employing the relation between $[\eta]$ and the molecular weight given in Part I (*loc. cit.*). This value is close to that obtained by Eley and Richards (*loc. cit.*) for $(E_p - E_t)$ in the stannic chloride-catalyzed polymerization of octyl vinyl ether, −3300 cal./mole.

If we assume, in view of the agreement between the two sets of results in Fig. 3, that this value also holds for the same stage in the aluminium chloride-catalyzed polymerization of styrene, then since $E = E_i + E_p - E_t - E_{st}$, where E is the overall energy of activation and E_i that for the initiation reaction and $E = 1200$ cal./mole (Part I, *loc. cit.*), it follows that $E_i = 5000$ cal./mole. The value of k_i obtained above would thus not appear to be attributable to a high energy of activation.

The Reaction Mechanism.—The absence of any co-catalyst in the reaction excludes the carbonium-ion theory of Polanyi and Skinner (*J.*, 1947, 257) and Plesch and Polanyi (*ibid.*, p. 252) for which the presence of a co-catalyst containing hydrogen is essential. A possible alternative mechanism might be based on catalyst interaction with the solvent (Pepper, *loc. cit.*), *viz.* :

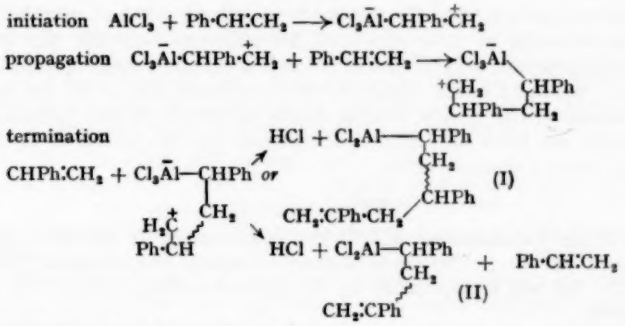
initiation $AlCl_3 + CCl_4 \longrightarrow AlCl_4^- \; CCl_3^+$

propagation $CCl_3^+ + Ph{\cdot}CH{:}CH_2 \longrightarrow Cl_3C{\cdot}CHPh{\cdot}CH_2^+$

termination $Cl_3C{\cdot}CHPh{\cdot}CH_2 \; . \; . \; . \; Ph{\cdot}CH{\cdot}CH_2^+ + AlCl_4^- \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2 \; . \; . \; . \; CPh{:}CH_2 + AlCl_3 + CCl_4$

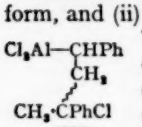
The objections to a scheme of this kind are so strong, however, that it must also be rejected. First, the catalyst is regenerated in an active form, and, secondly, the anion $AlCl_4^-$ should be capable of initiating polymerization in monomers with double bonds of electron-deficient character, *e.g.*, methyl methacrylate. We have found that aluminium chloride will not catalyze the polymerization of methyl methacrylate in carbon tetrachloride solution (see also Mayo and Lewis, *J. Amer. Chem. Soc.*, 1944, **66**, 1594). Also, this scheme leads to a kinetic expression for $-dM/dt$ which is not in agreement with equation (1), and to the presence of a double bond in each polymer molecule, which is contrary to our findings.

A reaction mechanism which is in agreement with all our results can, however, be based on the polarization of the monomeric double bond by the electrophilic catalyst, as already suggested by Price ("Reactions at Carbon–Carbon Double Bonds," Interscience Publ. Inc., 1946), *viz.* :



Subsequently, (I) and (II), which differ only in the degree of polymerisation, combine with hydrogen chloride, to give (III).

This mechanism satisfactorily explains (i) that catalyst is not regenerated in an active form, and (ii) that most of the polymer molecules do not contain an olefinic double bond. The presence of such a double bond in a small percentage of the molecules can be explained by the occasional non-recombination of the hydrogen chloride with the polymer. π-Complexes between Lewis acids and molecules containing conjugated systems are well known (see, *e.g.*, Dilke, Eley, and Perry, *Research*, 1949, **2**, 538). The objection raised by Plesch (*ibid.*, p. 267) to this type of mechanism, on the basis of the improbability of considerable charge separation in media of low dielectric constant, is over-ruled, since models of the polymers show that the ends of the chain can always readily take up a position of close proximity.



(III)

THE UNIVERSITY, NOTTINGHAM. [*Received, August 10th*, 1951.]

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113. *The Action of Ionizing Radiations and of Radiomimetic Substances on Deoxyribonucleic Acid. Part IV.* The Products of the Action of Di-(2-chloroethyl)methylamine.*†

By E. M. PRESS and J. A. V. BUTLER.

An examination has been made of the products formed when di-(2-chloroethyl)methylamine acts in dilute sodium hydrogen carbonate solutions on deoxyribonucleic acid of calf thymus. The main analytical difference between the product and the original nucleic acid is a decrease in the amount of primary amino-nitrogen and in that of purine nitrogen, precipitable as purine silver salt after hydrolysis with dilute sulphuric acid. The latter is appreciably greater than the total decrease of primary amino-nitrogen. Experiments have also been made on the action of the base on certain ribonucleosides.

IT has been shown (Part I, *J.*, 1950, 3411) that both di-(2-chloroethyl)methylamine and di-2-chloroethyl sulphide cause a "degradation" of the deoxyribonucleic acid of calf thymus in aqueous solutions of pH > 4, which is shown by the almost complete loss of the characteristic viscosity which occurs. In the case of the amine, it has been shown (Part III, *J.*, 1950, 3421) that the loss of viscosity is accompanied by a decrease of the apparent molecular weight. A knowledge of the chemical changes producing these physical effects would be of great interest, in view of the powerful biological actions of these and similar substances (see Part I for references) and the indications that deoxyribonucleic acids are particularly sensitive to them (Herriott, *J. Gen. Physiol.*, 1948, **32**, 221). The action of di-2-chloroethyl sulphide on thymonucleic acid was studied by Elmore, Gulland, Jordan, and Taylor (*Biochem. J.*, 1948, **42**, 308), who isolated two products of the reaction and from their titration curves concluded that the sulphur "mustard" had reacted with (1) the primary phosphoryl groups, (2) the purine-pyrimidine hydroxyl groups, together with (3) an uncertain amount of amino-groups. In order to interpret the physical effects reported in previous papers, and in view of the rather different conditions of the experiment of Elmore *et al.*, we have made a partial chemical examination of the products of the action of the amine on the nucleic acid in dilute sodium hydrogen carbonate. To assist this interpretation we have also made experiments on the action of di-(2-chloroethyl)-methylamine on some ribonucleosides.

EXPERIMENTAL

Preparation of the Thymonucleic Acid.—The preparations B and G/2 were prepared as described in Part I (*loc. cit.*). They were similar in physical properties and their analyses are given in Table 2. S/1 was a preparation by H. Schwander (Prep. VII) kindly given to us by Professor R. Signer.

* Part III, *J.*, 1950, 3421.

† Read, in abstract, at the XIIth International Congress of Pure and Applied Chemistry, New York, September 1951.

Preparation of the Reaction Product of Nucleic Acid with Di-(2-chloroethyl)methylamine.—*Preparation B/1.* 250 Mg. of the base were added to 200 mg. of nucleic acid in 200 ml. of 0·1N-sodium hydrogen carbonate saturated with chloroform in three portions during 72 hours at room temperature. After 24 hours more, the solution was dialysed for 6 days against frequent changes of distilled water at 2°. The dialysate was neutralised with acetic acid and concentrated to 25 ml. *in vacuo*. The residue was freeze-dried.

Preparation G/2/1. This was similarly prepared by adding, during 5 days, 600 mg. of base to 500 mg. of nucleic acid in 250 ml. of 0·1N-sodium hydrogen carbonate.

Preparation S/1/1 was similarly prepared by adding in two portions 300 mg. of base to 200 mg. of S/1 in 200 ml. of 0·1N-sodium hydrogen carbonate, followed by dialysis and freeze-drying.

Analytical.—Total nitrogen was determined by the micro-Kjeldahl method, and phosphorus colorimetrically by a modification of Martland and Robison's method (*Biochem. J.*, 1926, **20**, 847). Purine-nitrogen was determined by precipitation of the bases with saturated silver sulphate in dilute sulphuric acid at 2° (see Gulland, Jordan, and Threlfall, *J.*, 1947, 1129). Conditions of hydrolysis of the nucleic acid and time of digestion were varied as shown in the table. Finally, the second method of hydrolysis and digestion overnight were adopted for all determinations.

Results.

	Time of digestion, minutes	Purine-N, %	Pyrimidine-N, %	Recovery of total N, %
Hydrolysis 1. Solution of thymonucleic acid in 5·0% H_2SO_4 refluxed at 100° for 2 hours	60	8·7	5·7	95
	75	8·7	5·6	94
	90	9·05	6·0	99
	Overnight	9·05	5·9	98
Hydrolysis 2. Solution of thymonucleic acid in N-H_2SO_4 at 100° for 1 hour	40	7·7	5·6	89
	60	8·8	5·6	97
	90	9·0	6·0	99
	Overnight	9·0	6·0	99

The following results, obtained after hydrolysis of a mixture of purine and pyrimidine nucleosides, show that the method gives a quantitative precipitation of the purines under the conditions used :

	Mg. of N per ml. determined alone	Mg. of purine-N determined in mixture of 1 ml. of each	Mg. of pyrimidine-N determined in mixture of 1 ml. of each
Guanosine	0·195		
Adenosine	0·251	0·450	—
Cytidine	0·148	—	0·268
Thymine	0·115	—	

From a comparison of the results obtained with thymus deoxyribonucleic acid (Table 2) with those obtained recently with similar material, chromatographic methods being used to estimate the separate purines, it would appear that the silver method gives rather low values for the purines in the hydrolysis products of the natural nucleic acid (*e.g.*, Marshak and Vogel, *J. Biol. Chem.*, 1951, **189**, 597; Chargaff, Vischer, Doniger, Green, and Misani, *ibid.*, 1949, **177**, 405; Wyatt, *Biochem. J.*, 1951, **48**, 584). The values obtained by these workers for the ratio of purine-nitrogen to -phosphorus are in the region of 2·4—2·5 but the range of values is rather wide. Using the alternative copper hydrogen sulphite method of purine precipitation (Kerr and Blish, *J. Biol. Chem.*, 1932, **98**, 193; Kerr, *ibid.*, 1940, **132**, 147), we obtained the following results which are appreciably higher than those obtained by the silver method with the same preparation and higher than those reported by other authors (*loc. cit.*) :

	Purine N/P (± 0·09)		Purine N/P (± 0·09)
Nucleic acid B	2·68	Nucleic acid (preptn. B/1) treated with base	2·42

but a similar decrease of the precipitable purine after treatment with di-(2-chloroethyl)methylamine is observed.

It is concluded that, although the purine nitrogen/phosphorus ratio determined by the silver method may be somewhat low, the relative values obtained with the nucleic acids and their reaction products are significant.

Solubility of Silver Salts of Alkylated Purines.—The silver method of purine analysis depends on the fact that both guanine and adenine are quantitatively precipitated as silver salts in dilute

sulphuric acid. In order to find the effect of various substituents of the purine nucleus on the precipitability under these conditions a number of alkylated derivatives have been examined, with the results shown in Table 1. Results obtained with the simple purines are included to show the concentrations employed. The nucleic acid solutions were determined at a concentration equivalent to $7{\cdot}0 \times 10^{-4}$M with respect to purines.

It can be seen from this that methylation of guanine in the 1- or the 7-position does not interfere with the formation of an insoluble silver salt; in the xanthine series methylation in the 3-, the 3 : 7-, and the 1 : 3 : 7-positions and also in the 1 : 9- and the 1 : 3 : 9-positions prevents the formation of an insoluble silver salt, but with 1-, 7-, and 9-methyl- and 1 : 3- and 1 : 7-dimethyl-xanthine no precipitate is formed at the concentration normally used but may be formed at a higher concentration.

TABLE 1. *Precipitation of purine derivatives by saturated silver sulphate in dilute sulphuric acid.*

Base	Concn. (M)	H_2SO_4 concn. (M)	Recovery of N, %	Remarks
Guanine	$7{\cdot}0 \times 10^{-4}$	0·1—0·7	100	—
Adenine	$7{\cdot}0 \times 10^{-4}$	0·25—0·5	96	—
Hypoxanthine	$1{\cdot}0 \times 10^{-3}$	0·5	98	—
1-Methylguanine	$1{\cdot}2 \times 10^{-3}$	0·3	99	Ppt. did not dissolve when diluted 2-fold with N-H_2SO_4
7-Methylguanine	$1{\cdot}1 \times 10^{-3}$	0·3	98	As above
1 : 7-Dimethylguanine	$1{\cdot}0 \times 10^{-3}$	0·3	85	As above. This compound is possibly impure
1-Methylxanthine	$1{\cdot}6 \times 10^{-3}$ (sat.	0·5	—	No ppt. at room temp.; ppt. formed in 1 hr. at 2° which dissolves on 4-fold dilution
1 : 3-Dimethylxanthine	$1{\cdot}7 \times 10^{-3}$	0·3	—	No ppt. at 2°
,,	$1{\cdot}4 \times 10^{-2}$	0·5	—	Ppt. at 2° which dissolves on 2-fold dilution
3 : 7-Dimethylxanthine	$4{\cdot}3 \times 10^{-3}$ (sat.)	0·5	—	No ppt. after 24 hr. at 2°
1 : 3 : 7-Trimethylxanthine	$3{\cdot}3 \times 10^{-2}$	0·5	—	,, ,,
3-Methylxanthine	$7{\cdot}7 \times 10^{-4}$ (sat.)	0·3	—	No ppt. after 48 hr. at 2°
7-Methylxanthine	$2{\cdot}4 \times 10^{-3}$	0·3	79	No ppt. at room temp., ppt. at 2°
	$1{\cdot}8 \times 10^{-2}$	0·3	46	
9-Methylxanthine	$2{\cdot}2 \times 10^{-3}$	0·3	58	,, ,, ,,
	$1{\cdot}1 \times 10^{-2}$	0·5	—	No ppt. at 2°
1 : 7-Dimethylxanthine	$2{\cdot}3 \times 10^{-3}$	0·3	32	No ppt. room temp.; ppt. at 2°
1 : 9-Dimethylxanthine	$3{\cdot}9 \times 10^{-3}$	0·5	—	No ppt. after 48 hr. at 2°
1 : 3 : 9-Trimethylxanthine	$2{\cdot}0 \times 10^{-3}$	0·3	—	No ppt. after 48 hr. at 2°
Xanthosine	$1{\cdot}3 \times 10^{-3}$	0·3	—	,, ,,

Estimation of Deoxypentose by Diphenylamine Reaction.—Seibert's modification (*J. Biol. Chem.*, 1940, **133**, 594) of the original Dische reaction (*Mikrochemie*, 1930, **8**, 4) was employed.

Estimation of Free Amino-groups.—Van Slyke's method was used (*J. Biol. Chem.*, 1912, **12**, 275) with the reaction vessel due to Koch (*ibid.*, 1929, **84**, 601). For the nucleosides a reaction time of 70 minutes was found to be satisfactory. Nucleic acid was hydrolysed for 1 hour in N-sulphuric acid at 100° before estimation, and for reproducible results a reaction time of 2 hours was necessary.

Reaction of Di-(2-chloroethyl)methylamine with Nucleosides.—In view of the apparent loss of purine-nitrogen in the reaction with the nucleic acid, we have examined the reaction of the base with the purine nucleosides guanosine and adenosine and also with the pyrimidine nucleoside cytidine, under conditions similar to those employed with nucleic acid. These experiments were carried out with ribonucleosides derived from yeast, kindly given to us by Dr. R. J. C. Harris, since no deoxyribonucleosides were available.

Experiment I. Approx. 0·05% solutions of guanosine or adenosine in 0·1M-sodium hydrogen carbonate were kept for 4 days with the amine (12 mols. to 1 mol. of nucleoside) at room temperature, and the solution was made 1N with respect to sulphuric acid and heated for 20 minutes at 100°. Purine-nitrogen was then determined as described above. Control solutions of the nucleosides in sodium hydrogen carbonate were kept at room temperature for the same period, and the purine-nitrogen similarly estimated. The results are given in Table 3. In control experiments a 100% recovery of purine was obtained in the presence of the hydrolysis products of the amine. No purine was precipitated with silver sulphate when the treated nucleoside was not hydrolysed with sulphuric acid, and thus no free purine was liberated by the reaction of the nucleoside with the di-(2-chloroethyl)methylamine.

Experiment II. Adenosine.

A. 56·3 Mg in 5·5 ml. of 0·5M-sodium hydrogen carbonate were made up to 0·8M with sodium hydroxide and left at room temperature for 4 days.

A1. 2·5 Ml. of solution A were made up to 5 ml. with glacial acetic acid, and 2-ml. samples were used for estimation of primary amino-nitrogen. 0·2 Ml. was hydrolysed in N-sulphuric acid and purine-nitrogen estimated with silver sulphate.

A2. 2·5 Ml. of A were neutralised and brought up to N with concentrated sulphuric acid, heated for 1 hour at 100°, and made up to 5 ml. with water. 2 Ml. of this solution were used for determination of primary amino-nitrogen and 0·2 ml. for determination of purine-nitrogen.

B. 61·4 Mg. in 5·5 ml. of 0·5M-sodium hydrogen carbonate were made up to 0·8M with sodium hydroxide. 500 Mg. of amine were added, and the whole was left at room temperature for 4 days.

B1. 2·5 Ml. of solution B were made up to 5 ml. with glacial acetic acid and estimated as for A1.

B2. 2·5 Ml. of B were neutralised and made N with concentrated sulphuric acid, heated for 1 hour at 100°, and made up to 5 ml. with water; estimation was as for A2.

Cytidine. 118·1 Mg. of cytidine were dissolved in 15 ml. of 0·5M-sodium hydrogen carbonate, and 7·0 ml. of this solution were treated with 500 mg. of di-(2-chloroethyl)methylamine for 4 days at room temperature, and a further 7·0 ml. of the solution served as a control. Both solutions were then made up to 10·0 ml. with acetic acid, and 2·0-ml. samples of the solution used for estimation of primary amino-groups. Total nitrogen was determined on an acidified solution. Results are given in Table 4.

TABLE 2. *Action of di-(2-chloroethyl)methylamine (X) in* 0·1M-$NaHCO_3$ *on calf-thymus deoxypentosenucleic acid.*

	N, % (± 0·1)	P, % (± 0·2)	Purine-N, % (± 0·15)	Non-purine-N, % (± 0·1)	N/P * (± 0·08)	Deoxy P (± 5%)	Purine N * P (± 0·09)	Amino-N * P (± 0·06)
Nucleic acid B	14·8	9·0	8·75	5·7	3·66	6·6	2·13	0·79
Nucleic acid treated with (*X*) : B/1	14·4	8·15	6·55	8·0	3·92	6·8	1·76	0·79
Nucleic acid : G/2	15·6	9·15	9·5	6·1	3·79	—	2·30	0·79
								0·79
								0·83
Nucleic acid treated with (*X*) : G/2/1	14·4	7·6	6·2	7·6	4·21	—	1·81	0·71
								0·66
								0·72
Nucleic acid : S/1	14·6	8·8	9·1	5·4	3·68	—	2·29	0·82
								0·79
								0·82
Nucleic acid treated with (*X*) : S/1/1	14·6	7·8	6·7	7·6	4·15	—	1·9	0·74
								0·72

* Atomic ratios.

TABLE 3. *Experiment I. Treatment of purine nucleosides with di-(2-chloroethyl)methylamine in* 0·1M-$NaHCO_3$.

	Guanosine		Adenosine	
	Total N, % (± 0·1)	Purine-N, % (± 0·15)	Total N, % (± 0·1)	Purine-N, % (± 0·15)
In water	21·2	20·8	25·3	24·4
In $NaHCO_3$	—	20·7	—	24·3
Treated with amine for 4 days at room temp.	—	9·1	—	20·0
Decrease of purine-nitrogen	—	55%	—	18%

TABLE 4. *Experiment II. Decrease of primary amino-nitrogen in the reaction of adenosine and cytidine with di-(2-chloroethyl)methylamine.*

	Without hydrolysis		With hydrolysis	
	Primary amino-N, mg./ml.	Total purine-N, mg./ml.	Primary amino-N, mg./ml.	Total purine-N, mg./ml.
Adenosine (A)	0·27, 0·25	1·25	0·24	1·34
Adenosine + (*X*) (B)	0·12, 0·11	0·80	0·11, 0·10	0·90
Decrease (%)	63	42	60	41

	Primary amino-N, mg./ml.	Total N, mg./ml.
Cytidine	0·26, 0·24	0·78
Cytidine + (*X*)	0·19, 0·19	—
Decrease (%)	24	—

Results. (i) *Dialysate.* It was shown (Part III, *loc. cit.*) that the product of this reaction contains a proportion of material of low molecular weight. This is confirmed by the fact that on dialysis both organic nitrogen and phosphorus pass through the membrane and a deoxypentose sugar and a purine base can be detected in the dialysate. The total amount dialysing is, however, only about 2% of the starting material. The dialysate is comparatively rich in purines, the atomic ratio of purine-N to -P being 9·5.

(ii) *Inorganic phosphorus.* After treatment with di-(2-chloroethyl)methylamine, as described, the nucleic acid solution contained no inorganic phosphate even after 3 weeks at room temperature. After this period the whole of the phosphorus was still precipitable by 0·25% uranyl acetate in 2·5% trichloroacetic acid (Macfadyen, *J. Biol. Chem.*, 1934, **107**, 299).

(iii) *Analysis of non-dialysable product.* Table 2 shows the analytical results obtained with three distinct preparations, made from different samples of the nucleic acid. The last four columns represent total nitrogen, deoxypentose sugar, purine nitrogen, and primary amino-nitrogen expressed as proportions of the amount of phosphorus present. From the N/P ratios it is found that the amount of residues of the amine attached to the nucleic acid is about one per tetranucleotide in the first preparation and rather more (*ca.* 1·4) in the others. This amount is not known with high precision since the addition of one residue per tetranucleotide causes an increase of the N/P ratio of only 7%, whereas the overall accuracy of the determinations is of the order of ±2%.

The main features of these results are as follows: (1) there is no change in the ratio of deoxypentose sugar to phosphorus as determined by the diphenylamine colour reaction; (2) the amount of purine precipitable as silver salt is diminished by the reaction, and the decrease is significantly greater than the decrease of primary amino-nitrogen determined by the van Slyke method.

It is evident from this that di-(2-chloroethyl)methylamine is capable of reacting with the purine groups of the nucleic acid, and the reaction product survives hydrolysis. The fact that the decrease of purine nitrogen observed is appreciably greater than the decrease of free amino-nitrogen (which includes also whatever effect the reaction of the amine has had on the cytidine amino-group) would appear to show that some reaction with the purines has occurred in other ways than with their primary amino-groups.

(iv) *Riboside experiments.* It is seen (Table 3) that treatment with the amine of both guanosine and adenosine causes an appreciable decrease in the amount of purine-nitrogen. Table 4 shows a comparison of the decrease in primary amino-nitrogen with the corresponding decrease of purine-nitrogen for adenosine with the amine. In view of the fact that the primary amino-determinations of the treated nucleic acid were made after hydrolysis in N-sulphuric acid, it seemed desirable to make the determination with the nucleoside under the same conditions.

It can be seen from the figures that the primary amino-nitrogen determined in the treated nucleoside is the same before and after hydrolysis. It is therefore clear that the decrease in the value of the primary amino-nitrogen caused by the reaction of di-(2-chloroethyl)methylamine is not due to a blockage of the free amino-groups which can be removed by hydrolysis. The decrease of primary amino-nitrogen of adenosine is appreciably greater than the loss of purine-nitrogen under the same reaction conditions. The experiment with the pyrmidine nucleoside cytidine also shows that reaction involving the primary amino-groups has taken place.

The determination of the free amino-nitrogen of guanosine is difficult both on account of its low solubility and because it is known (van Slyke, *J. Biol. Chem.*, 1911, **9**, 183) to give results in the van Slyke apparatus which are 25% too high. No comparison was made in this case.

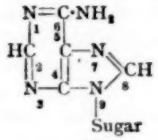
In order to find if the apparent loss of purine was due to a radical change in the purine groups or merely to their substitution, we examined the ultra-violet absorption curves of the solutions of experiment I (above). The measurements were made at a dilution of 33·3 in the medium named. The absorption curves in the region of the main absorption band (230—280 mμ) are not greatly affected, as they might be expected to be if the purine nucleus were changed fundamentally, but the following figures show that maximum of absorption is displaced towards longer wave-lengths by treatment with the amine:

	Maximum of absorption, mμ	pH
Guanosine in $NaHCO_3$ (0·1N)	254	8·71
Guanosine in H_2SO_4 (N)	257	—
Guanosine after treatment with amine in $NaHCO_3$ (0·1N)	270	8·62
Guanosine after treatment with amine in H_2SO_4 (N)	268	
Hydrolysis product of guanosine in H_2SO_4 (N) (guanine)	248	—
Hydrolysis product of treated guanosine in H_2SO_4 (N)	261	—

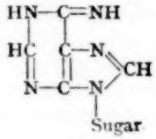
The displacement of the absorption maximum persists after hydrolysis. These displacements would appear to be due to a loading of the purine nucleus with substituents, similar to the effect of the addition of the ribose sugar to guanine. It can be inferred from this, though perhaps not with certainty, that the purine nucleus remains intact.

Discussion

It has been shown that in the reaction of di-(2-chloroethyl)methylamine with the nucleic acid and with the purine ribonucleosides the amount of " purine " precipitable as the silver salt in acid solution is decreased. The extent of the modification of the purine group required to affect non-precipitation in this process is not clearly known. In our experiments it has been found that methylation of guanine in the 1- or the 7-position does not interfere, but in xanthine derivatives methylation in various positions such as the 3- and 7-, and 1-, 3-, and 7-, either completely or partly prevents the precipitation. Although no general rule can be drawn from this, it may reasonably be concluded that the decrease of purine nitrogen observed is due to alkylation of adenosine or guanosine.



(I)



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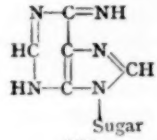

(III)

In the case of adenosine (I), which can also react in the tautomeric forms (II) and (III), it can be seen that every possible reaction involves a loss of primary amino-nitrogen, but only when reaction has occurred in forms (II) and (III) will the ring nitrogen atoms 1 and 3 be alkylated. It is therefore possible in the reaction with adenosine for the decrease of primary amino-nitrogen to be greater than the loss of " purine-nitrogen," as is found to be the case.

On the other hand, with guanosine, there are other possibilities in that (in the keto-form) either of the nitrogen atoms in positions 1 and 3 can be alkylated without the primary amino-group in position 2 being affected. In this case a loss of purine-nitrogen might be possible without any decrease of free amino-group. It would appear from this that the excess of the decrease of purine-nitrogen over that of primary amino-nitrogen in the treated nucleic acid must be due to alkylation of the ring nitrogen atoms of guanosine in this way. It is interesting to note that Fruton, Stein, and Bergmann (*J. Org. Chem.*, 1946, **11**, 559) found that when histidine is treated with various nitrogen " mustards," the attack is on the glyoxaline ring to a greater extent than on the primary amino-group. In the case of cytidine, every possible reaction with di-(2-chloroethyl)-methylamine results in a loss of primary amino-nitrogen, and the reaction occurs to an appreciable extent with free cytidine (Table 4). Since the loss of primary amino-groups in the treated nucleic acid is small (*ca.* 10% of the total present), it follows that the amine can have reacted with the adenine and cytosine groups of nucleic acid to only a very limited extent.

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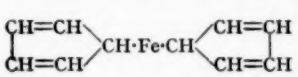
114. *Dicyclopentadienyliron.*

By Samuel A. Miller, John A. Tebboth, and John F. Tremaine.

Reduced iron (in presence of alumina and potassium oxide, and preferably also molybdenum oxide) reacts with *cyclo*pentadiene in nitrogen at 300° to give a yellow compound $C_{10}H_{10}Fe$, m. p. 172·5—173°, believed to be di*cyclo*pentadienyliron. It sublimes above 100° without decomposition, is volatile in steam, and soluble in organic solvents. The formation of this compound proceeds only for 10—15 minutes, after which further reaction is only effected after careful oxidation and re-reduction of the iron. After being heated in a glass tube at 250° in nitrogen, and frequently as first prepared, the iron compound contains small amounts of adsorbed nitrogen which is sufficiently firmly held to give positive sodium-fusion tests for nitrogen. It has not been possible to use this property to make the material behave as a catalyst for ammonia formation.

Compounds containing only carbon, hydrogen, and iron have not hitherto been described, and the direct replacement of hydrogen attached to carbon by iron would not be expected to be feasible. It has now been found that reduced iron, in the form of the well-known "doubly-promoted synthetic ammonia catalyst," can be made to react with *cyclo*pentadiene in nitrogen at 300° and at atmospheric pressure, to give a yellow crystalline compound, of composition $C_{10}H_{10}Fe$. The iron is in its bivalent form, since treatment of a carbon tetrachloride solution of the material with bromine in the same solvent gave a dark green precipitate, which dissolved in water to give a blue solution containing ferrous and bromide ions. The structure of the compound has not been further elucidated, but by analogy with the well-known *cyclo*pentadienylpotassium, it is believed that substitution has occurred in the methylene group, and that the compound has the structure inset.



The compound melts without decomposition at 172·5—173° and sublimes readily, still without decomposition. It is soluble in alcohol, ether, and benzene, but not in water. On concentration of an alcoholic solution on the water-bath, the compound distils in the alcohol vapour; it is also steam-volatile. It is charred by and reduces sulphuric acid, and decolorises acid potassium permanganate.

The conversion of the reduced iron into di*cyclo*pentadienyliron, when a stream of nitrogen containing *cyclo*pentadiene vapour is passed over it, proceeds only for 10—15 minutes. The residual reduced iron is then unchanged in regard to its activity as a catalyst with respect to the synthesis of ammonia at 550°, and the reason for the inhibition of further formation of the iron derivative has not been elucidated. It is possible to revivify the iron by oxidation at 450° in an atmosphere of nitrogen containing steadily increasing proportions of oxygen, and finally in air, and then reduction at 450°. The revivified product can then again be made to produce di*cyclo*pentadienyliron for 10—15 minutes only.

The initial rate of production of iron di*cyclo*pentadienyl, and the total period of reaction before inhibition sets in, can both be increased, resulting in about a 3-fold increase in output, by the addition of 1% of molybdenum oxide to the doubly-promoted catalyst.

A curious feature of several of the preparations of di*cyclo*pentadienyliron was that the crude products contained nitrogen and gave positive results in the Lassaigne test. Purification always resulted in a product free from nitrogen. In view of this capacity to adsorb nitrogen at comparatively low temperatures, some experiments were carried out with 3 : 1 mixtures of hydrogen and nitrogen under a variety of conditions, but the compound was not capable of acting as a vapour-phase catalyst for ammonia synthesis.

Experimental

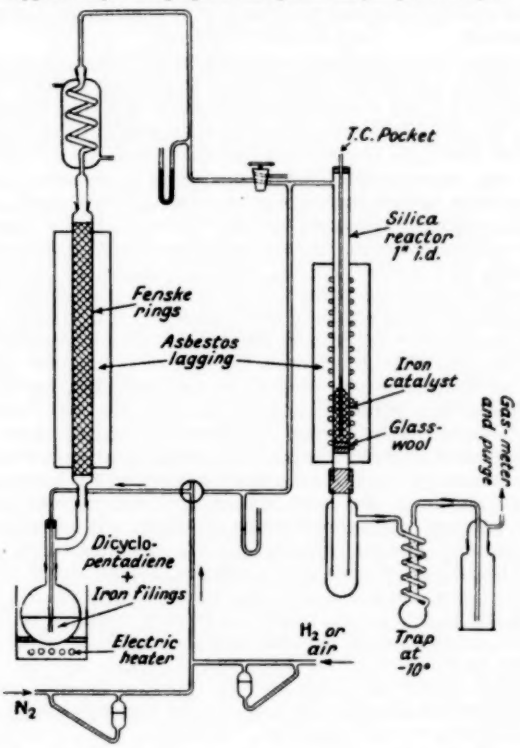
Preparation of Dicyclopentadienyliron.—The following series of preparations with one specimen of catalyst was carried out after preliminary experiments establishing the formation

of the product and its nature, the rapid failing of reactivity of the reduced iron, and the practicability of revivification.

Ferric nitrate (3 kg.) and a aluminium nitrate (300 g.) were dissolved in distilled water (4 l.), and treated with the equivalent of potassium hydroxide as a 40% solution. The precipitate was separated on the centrifuge, and washed *in situ* with distilled water (5 l.). It was dried at 100° for 4 hours, and then ignited at 600° in a muffle furnace for 10 hours. As it still contained 10·7% of water-soluble material (calculated as K_2CO_3), it was washed with 2-l. portions of distilled water, dried again, and then converted into $\frac{1}{8}$"-diameter pellets. Analysis then showed: Fe_2O_3, 90·1; FeO, 1·4; Al_2O_3, 6·9; water-solubles (as K_2CO_3), 1·3; moisture, 0·3%.

40 Ml. of the unreduced pellets were charged into the 1"-diameter silica reactor tube of the apparatus shown in the accompanying diagram, and reduced during 10 hours at 450° in a

Apparatus for the preparation of iron dicyclopentadienyl.



50 l./hour stream of dry hydrogen. A short test was then carried out, by passing a 1 : 3 mixture of nitrogen and hydrogen through the reactor at 550°, to confirm the activity of the reduced iron as a catalyst for the synthesis of ammonia.

It was found to be most convenient to prepare *cyclo*pentadiene as required from its dimer. This was boiled with a little iron filings, and a stream of nitrogen passed through it, and the issuing mixture of monomer and dimer passed up through the fractionating column (see figure) surmounted by a reflux condenser. The nitrogen issuing from the top of the reflux condenser was regarded as being saturated with *cyclo*pentadiene at the temperature of the cooling water. For the present series of experiments, the nitrogen was fed at 25 l./hour, the condenser kept at 15°, and the reactor at 300°.

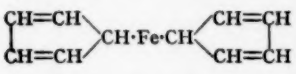
After the first reaction with *cyclo*pentadiene, the reactor was purged with nitrogen, and then mixtures of nitrogen and air were passed through it at 25 l./hour. In order to avoid developing high temperatures on the catalyst surface, the air content of the mixture was increased slowly, in 5 half-hourly steps as 5, 10, 20, 40, and 100% of air, and the temperature was gradually

114. *Dicyclopentadienyliron.*

By Samuel A. Miller, John A. Tebboth, and John F. Tremaine.

Reduced iron (in presence of alumina and potassium oxide, and preferably also molybdenum oxide) reacts with *cyclo*pentadiene in nitrogen at 300° to give a yellow compound $C_{10}H_{10}Fe$, m. p. 172·5—173°, believed to be di*cyclo*pentadienyliron. It sublimes above 100° without decomposition, is volatile in steam, and soluble in organic solvents. The formation of this compound proceeds only for 10—15 minutes, after which further reaction is only effected after careful oxidation and re-reduction of the iron. After being heated in a glass tube at 250° in nitrogen, and frequently as first prepared, the iron compound contains small amounts of adsorbed nitrogen which is sufficiently firmly held to give positive sodium-fusion tests for nitrogen. It has not been possible to use this property to make the material behave as a catalyst for ammonia formation.

Compounds containing only carbon, hydrogen, and iron have not hitherto been described, and the direct replacement of hydrogen attached to carbon by iron would not be expected to be feasible. It has now been found that reduced iron, in the form of the well-known "doubly-promoted synthetic ammonia catalyst," can be made to react with *cyclo*pentadiene in nitrogen at 300° and at atmospheric pressure, to give a yellow crystalline compound, of composition $C_{10}H_{10}Fe$. The iron is in its bivalent form, since treatment of a carbon tetrachloride solution of the material with bromine in the same solvent gave a dark green precipitate, which dissolved in water to give a blue solution containing ferrous and bromide ions. The structure of the compound has not been further elucidated, but by analogy with the well-known *cyclo*pentadienylpotassium, it is believed that substitution has occurred in the methylene group, and that the compound has the structure inset.



The compound melts without decomposition at 172·5—173° and sublimes readily, still without decomposition. It is soluble in alcohol, ether, and benzene, but not in water. On concentration of an alcoholic solution on the water-bath, the compound distils in the alcohol vapour; it is also steam-volatile. It is charred by and reduces sulphuric acid, and decolorises acid potassium permanganate.

The conversion of the reduced iron into di*cyclo*pentadienyliron, when a stream of nitrogen containing *cyclo*pentadiene vapour is passed over it, proceeds only for 10—15 minutes. The residual reduced iron is then unchanged in regard to its activity as a catalyst with respect to the synthesis of ammonia at 550°, and the reason for the inhibition of further formation of the iron derivative has not been elucidated. It is possible to revivify the iron by oxidation at 450° in an atmosphere of nitrogen containing steadily increasing proportions of oxygen, and finally in air, and then reduction at 450°. The revivified product can then again be made to produce di*cyclo*pentadienyliron for 10—15 minutes only.

The initial rate of production of iron di*cyclo*pentadienyl, and the total period of reaction before inhibition sets in, can both be increased, resulting in about a 3-fold increase in output, by the addition of 1% of molybdenum oxide to the doubly-promoted catalyst.

A curious feature of several of the preparations of di*cyclo*pentadienyliron was that the crude products contained nitrogen and gave positive results in the Lassaigne test. Purification always resulted in a product free from nitrogen. In view of this capacity to adsorb nitrogen at comparatively low temperatures, some experiments were carried out with 3 : 1 mixtures of hydrogen and nitrogen under a variety of conditions, but the compound was not capable of acting as a vapour-phase catalyst for ammonia synthesis.

Experimental

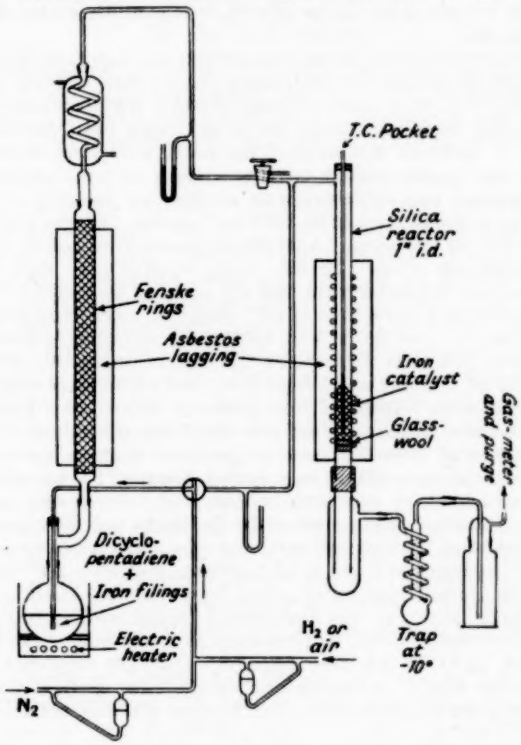
Preparation of Dicyclopentadienyliron.—The following series of preparations with one specimen of catalyst was carried out after preliminary experiments establishing the formation

of the product and its nature, the rapid failing of reactivity of the reduced iron, and the practicability of revivification.

Ferric nitrate (3 kg.) and a aluminium nitrate (300 g.) were dissolved in distilled water (4 l.), and treated with the equivalent of potassium hydroxide as a 40% solution. The precipitate was separated on the centrifuge, and washed *in situ* with distilled water (5 l.). It was dried at 100° for 4 hours, and then ignited at 600° in a muffle furnace for 10 hours. As it still contained 10·7% of water-soluble material (calculated as K_2CO_3), it was washed with 2-l. portions of distilled water, dried again, and then converted into ⅛"-diameter pellets. Analysis then showed: Fe_2O_3, 90·1; FeO, 1·4; Al_2O_3, 6·9; water-solubles (as K_2CO_3), 1·3; moisture, 0·3%.

40 Ml. of the unreduced pellets were charged into the 1"-diameter silica reactor tube of the apparatus shown in the accompanying diagram, and reduced during 10 hours at 450° in a

Apparatus for the preparation of iron dicyclopentadienyl.



50 l./hour stream of dry hydrogen. A short test was then carried out, by passing a 1 : 3 mixture of nitrogen and hydrogen through the reactor at 550°, to confirm the activity of the reduced iron as a catalyst for the synthesis of ammonia.

It was found to be most convenient to prepare *cyclo*pentadiene as required from its dimer. This was boiled with a little iron filings, and a stream of nitrogen passed through it, and the issuing mixture of monomer and dimer passed up through the fractionating column (see figure) surmounted by a reflux condenser. The nitrogen issuing from the top of the reflux condenser was regarded as being saturated with *cyclo*pentadiene at the temperature of the cooling water. For the present series of experiments, the nitrogen was fed at 25 l./hour, the condenser kept at 15°, and the reactor at 300°.

After the first reaction with *cyclo*pentadiene, the reactor was purged with nitrogen, and then mixtures of nitrogen and air were passed through it at 25 l./hour. In order to avoid developing high temperatures on the catalyst surface, the air content of the mixture was increased slowly, in 5 half-hourly steps as 5, 10, 20, 40, and 100% of air, and the temperature was gradually

raised, but never allowed to reach 450°. Oxidation was considered complete when the measured temperature kept quite steady with 100% air passing. The reactor was then flushed out with nitrogen, and hydrogen passed through at 50 l./hour for 12 hours at 450°. A further experiment with nitrogen and *cyclo*pentadiene was then carried out.

The product in each case was washed out of the receiver with ether, and the ether evaporated off under reduced pressure. Some of the *cyclo*pentadiene was recovered in the cold trap. Conversion of *cyclo*pentadiene into its iron compound could only be estimated approximately, but during the 15-minute periods of activity, the conversion amounted to 40—50%.

The following amounts of product were isolated in 15 successive experiments with the same charge of iron pellets: 0·93, 0·88, 1·01, 1·10, 1·08, 0·96, 0·53, 1·04, 0·35, 0·98, 0·61, 0·31, 0·97, 0·41, 0·75 g., giving in all 11·91 g. In the ninth cycle the oxidation had been omitted, the pellets being only treated with hydrogen for 2 hours. Although on three other occasions the full revivification procedure also only gave small amounts of product (0·31—0·53 g.), and no explanation for these low amounts can be offered, it is considered that revivification without oxidation was less efficient.

Experiment in Presence of Molybdenum.—A solution was prepared of ferric nitrate (650 g.), aluminium nitrate (29 g.), ammonium molybdate (13 g.), and distilled water (500 ml.), and potassium hydroxide (0·6 g.) in a small quantity of water was then added. The solution was stirred, and concentrated aqueous ammonia was added slowly until the mixture was alkaline to litmus. The excess of ammonia and most of the water were then evaporated off to leave a pasty mass, which was gently heated on a sand-bath to complete the decomposition of ammonium salts; copious nitrous fumes were evolved at this stage. The resulting black residue was ignited in a muffle furnace at 600° for 6 hours. It was then formed into pellets ($\frac{3}{8}$") and reduced at 450° in hydrogen. Analysis of the material before reduction showed that after reduction the composition was: Fe, 90; Al_2O_3, 8; Mo_2O_3, 1; K_2O, 1%.

The apparatus used in this experiment was the same as that shown in the above diagram except that the reactor was a silica tube of 0·6" diameter. On passage of nitrogen saturated with *cyclo*pentadiene at 15° over the iron at 300°, there was considerable formation of yellow crystals in the receiver, but after 15 minutes the rate of production dropped rapidly. The total solid obtained in 25 minutes was 3·0 g., compared with the average of 1 g. obtained in absence of the molybdenum. Reduced iron prepared in the way just described but with omission of the molybdenum gave only a trace of di*cyclo*pentadienyliron.

Attempted Preparation at High Pressures.—A number of attempts were made to prepare larger amounts of material by reaction in a heated rotating 1-l. autoclave. These included starting with *cyclo*pentadiene or di*cyclo*pentadiene, and the reduced doubly-promoted iron catalyst, iron filings, " Raney " iron (obtained by dissolving out the aluminium from an iron–aluminium alloy) with and without ethanol, and the material containing molybdenum as described above, and heating in nitrogen at 12—150 atm. and 200—300° for $\frac{1}{2}$—2 hours. Small quantities of yellow or brown oils containing iron were obtained which were soluble in alcohol and volatile in its vapour, but in no case could di*cyclo*pentadienyliron be isolated.

Analyses.—*Dicyclopentadienyliron*, recrystallised from aqueous ethanol, had m. p. 172·5—173° (Found: C, 64·4, 65·2; H, 5·5, 5·8; Fe, 29·9. $C_{10}H_{10}Fe$ requires C, 64·5; H, 5·4; Fe, 30·1%). The molecular weight as determined by the Rast method gave high and erratic results, but ebullioscopically in benzene values of 210 and 175 were obtained ($C_{10}H_{10}Fe$ requires *M*, 186).

Reaction for Nitrogen.—Several of the specimens of crude product gave positive tests for nitrogen by the sodium-fusion method, but quantitative determination by micro-Kjeldahl or micro-Dumas methods was not possible. Purified specimens usually did not contain nitrogen even by the Lasaigne test. A specimen of this nitrogen-free, purified di*cyclo*pentadienyliron was heated in a Carius tube for one hour at 250—300° in an atmosphere of nitrogen; the resulting material gave a positive test for nitrogen. Another specimen was similarly heated in an atmosphere of ammonia, but the resulting material did not give a positive test for nitrogen. Another specimen was heated in a glass bulb in an atmosphere of nitrogen attached to a manometer; at 100° there was a reduction of pressure corresponding to absorption of 1·0 ml. of nitrogen per g. of di*cyclo*pentadienyliron, but at higher temperatures the material sublimed out of the hot zone into the manometer.

Di*cyclo*pentadienyliron was heated to 100—150° in nitrogen at 10 atm. in a small steel bomb (7-ml. capacity; 40 g. tare weight). There was no detectable adsorption of nitrogen. It is possible that this adsorption occurs in glass but not in steel apparatus.

Tests as an Ammonia Catalyst.—Mixtures of hydrogen and nitrogen (3 : 1) were heated in

an autoclave with di*cyclo*pentadienyliron at 20—50 atm. and 100—250°, but no ammonia was obtained. A similar negative result was found when di*cyclo*pentadienyliron vapour at various concentrations in a stream of nitrogen and hydrogen was passed through Pyrex tubes at 300° and 400°.

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115. *The Preparation of* p-*Dimethylaminoacetophenone and its Homologues.*

By A. W. NINEHAM.

The preparation is described of *p*-dimethylaminoacetophenone and its homologues in acceptable yields from readily available starting materials. The orientation of some new homologues is established, and a previous description of *p*-dimethylaminopropiophenone is shown to be erroneous.

METHODS for the preparation of *p*-dimethylaminoacetophenone have been reported by Weil (*Monatsh.*, 1908, **29**, 906), Staudinger and Kon (*Annalen*, 1911, **384**, 111), Hurd and Webb (*J. Amer. Chem. Soc.*, 1927, **49**, 551), von Braun and Weissbach (*Ber.*, 1930, **63**, 493), Kumler (*J. Amer. Chem. Soc.*, 1946, **68**, 1184), and Haddow *et al.* (*Phil. Trans.*, 1948, *A*, **241**, 147). In the first three cases yields were poor; in the last two no details or yields were given. Since the present work was carried out, a preparation in 70% yield from *p*-nitroacetophenone by reductive methylation has been described (Pearson and Bruson, *J. Amer. Chem. Soc.*, 1951, **73**, 864) but the unavailability of starting materials prevents its general application to homologues. There is one report (Skraup and Nieten, *Ber.*, 1924, **57**, 1294) which claims *p*-dimethylaminopropiophenone, but the present work seems to show this claim to have been erroneous and that small yields of mixed *ortho*- and *para*-isomers appear to have been produced by the two methods described. No other homologues have been reported. The general procedure for the preparation of aromatic ketones described by Kosolapoff (*J. Amer. Chem. Soc.*, 1947, **69**, 1651) has now been successfully applied to dimethylaniline and diethylaniline. Workable yields have been obtained in the former case by using acetic, propionic, *n*-butyric, and *n*-valeric acids, to give *p*-dimethylamino-acetophenone, -propiophenone, -butyrophenone, and -valerophenone, and in the latter case by using acetic acid to give *p*-diethylaminoacetophenone. The temperature of refluxing dimethylaniline appeared to be optimum and the use of light petroleum (b. p. 60—80°) was unsatisfactory.

The product described by Skraup and Nieten (*loc. cit.*) as *p*-dimethylaminopropiophenone was a yellow oil, boiling at 270—272°, forming a phenylhydrazone, m. p. 58°. No analysis of either product was recorded. *p*-Dimethylaminopropiophenone prepared as described above was closely similar to *p*-dimethylaminoacetophenone in properties. The evidence of the present work seems clearly to confirm that the compound derived from dimethylaniline and propionic acid has the structure claimed: its behaviour is similar to that of the known acetophenone homologue, and it yields a phenylhydrazone, hydrazone, and azine, and a quaternary salt with methyl iodide. The orientation of the compound was established in two ways. First, reduction with hydrazine and ethylene glycol gave *p*-*n*-propyldimethylaniline, which was quaternised with methyl iodide, the product not depressing the melting point of authentic trimethyl-*p*-*n*-propylphenylammonium iodide (Cull, Davies, and Hulbert, *J. Soc. Chem. Ind.*, 1938, 349). Secondly, the ketone was reduced by lithium aluminium hydride to the secondary carbinol which did not depress the melting point of authentic 1-*p*-dimethylaminophenylpropanol (Sachs and Sachs, *Ber.*, 1905, **38**, 514). Attempts to orientate the compound by oxidation were unsuccessful. Clemmensen reduction led to what appeared to be a mixture of *p*-*n*-propylaniline and 3 : 4-bis-*p*-dimethylaminophenylhexane-3 : 4-diol. Skraup and Nieten's compound was found to give a phenyl-

hydrazone, m. p. 60—60·5° (lit., m. p. 58°), which gave analyses satisfactory for that of dimethylaminopropiophenone and may be the *ortho*-isomer. Small amounts of this material, yielding the same phenylhydrazone, were isolated from our phosphoric oxide condensations.

p-Dimethylaminopropiophenone was also obtained in 12% yield by condensation of propionic anhydride with dimethylaniline and anhydrous aluminium chloride in carbon disulphide. The orientation of *p*-dimethylaminobutyrophenone was also established by reduction with lithium aluminium hydride to 1-*p*-dimethylaminophenylbutanol which did not depress the melting point of a sample obtained by treating *p*-dimethylaminobenzaldehyde with *n*-propylmagnesium bromide.

Experimental

p-*Dimethylaminoacetophenone.*—Redistilled dimethylaniline (300 g.) was stirred in a 1-l. 3-necked flask, and glacial acetic acid (60 g., 1 mol.) run in. " Hyflo Supercel " (4 g.) was added, followed by phosphoric oxide (75 g.) which caused the mixture to become hot. It was refluxed (at about 170—200°) for 45 minutes, with stirring, poured on ice, and rendered alkaline to litmus. After filtration, the solution was extracted with benzene, washed with water, and dried, and the solvent removed. The residue was distilled, giving unchanged dimethylaniline, b. p. <100°/15 mm., a mixture of the product with a little dimethylaniline, b. p. 110—150°/15 mm., and the desired product, b. p. 155—165°/12 mm., which solidified in the receiver. Distillation was stopped, and the residue in the flask crystallised. The collected solids were crystallised from light petroleum (b. p. 60—80°), then having m. p. 102° (40 g., 25% based on the acetic acid used). Recrystallisation from light petroleum (b. p. 60—80°) gave *p*-dimethylaminoacetophenone, m. p. 103—103·5° (corr.) (Found: N, 8·7. Calc. for $C_{10}H_{13}ON$: N, 8·7%). An alternative method of working up, in which the dimethylaniline was removed by steam-distillation, gave somewhat lower yields, probably because the product is somewhat steam-volatile. In this procedure, the residue was crystallised from light petroleum and the mother-liquors were found to contain considerable quantities (nearly equal in weight to that of the product) of by-products, which were not fully examined, but did contain a small amount of, probably, *o*-dimethylaminoacetophenone.

p-*Dimethylaminoacetophenoneazine*, prepared from the ketone and 50% hydrazine hydrate, formed flat orange leaflets, m. p. 259—260°, from 2-ethoxyethanol or nitrobenzene (Found: N, 17·5. $C_{20}H_{26}N_4$ requires N, 17·4%). By using half the amount of ketone in the same preparation, the unstable *hydrazone*, sintering at 95° (decomp.), was obtained in 84% yield as a colourless crystalline mass (Found: N, 22·6. $C_{11}H_{18}N_3$ requires N, 23·7%).

p-*Dimethylaminopropiophenone.*—(*a*) The two procedures of Skraup and Nieten (*loc. cit.*) were followed; that involving the use of *p*-dimethylaminophenylmercuric chloride gave the result reported in their work.

In the alternative, propionyl chloride (117 g.) was refluxed overnight with redistilled dimethylaniline (339 g.) and powdered anhydrous zinc chloride (60 g.). The decanted liquors were distilled, giving a small fore-run, b. p. <120°. The residue was treated with aqueous sodium hydroxide, dimethylaniline removed by steam-distillation, and the residue, after ether-extraction and drying, was distilled giving a light yellow oil, b. p. 175—180/32 mm., a deeper yellow oil, b. p. up to 135°/1·5 mm., and a viscous orange oil, b. p. 140—145°/0·1 mm., which solidified in the receiver. A large residue (150 c.c.) remained undistilled. The first fraction, with phenylhydrazine, gave a solid, crystallising slowly from dilute acetic acid, or methanol, forming highly refractive colourless rectangular plates, m. p. 60—65°, which gave analyses for the *phenylhydrazone* of a dimethylaminopropiophenone, possibly the *ortho*-isomer (Found: N, 15·7. $C_{17}H_{21}N_3$ requires N, 15·7%). The second fraction partly solidified when kept and was filtered; the solid, crystallised from methanol and then from light petroleum (b. p. 40—60°), had m. p. 58—58·5° and was *N*-methylpropionanilide (lit., m. p. 58·5°) (Found: C, 73·3; H, 8·0; N, 9·1. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%). The third fraction, crystallised from methanol, had m. p. 101° and was *p*-dimethylaminopropiophenone (5 g.) (see below).

(*b*) Redistilled dimethylaniline (600 g., 5 moles), propionic acid (148 g., 2 moles), and " Hyflo Supercel " (8 g.) were stirred and treated with phosphoric oxide (156 g., 1·1 moles), giving, by the procedure described for *p*-dimethylaminoacetophenone, p-*dimethylaminopropiophenone* (98 g., 55% based on the propionic acid used), which crystallised in shining plates, m. p. 103°, from light petroleum (b. p. 60—80°) (Found: C, 74·8; H, 8·6; N, 8·1. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·4; N, 7·9%). The product did not depress the m. p. of the product, m. p. 101°, recorded under (*a*).

The ketone was converted into *trimethyl-p-propionylphenylammonium iodide*, colourless prisms (from ethanol), m. p. 145° (Found : I, 39·4. $C_{12}H_{18}ONI$ requires I, 39·8%).

The *phenylhydrazone*, prepared in warm 50% acetic acid, crystallised from methanol in red prisms, m. p. 137—138°, which decomposed when kept for 3 weeks (Found : N, 15·7. $C_{17}H_{21}N_3$ requires N, 15·7%).

p-Dimethylaminopropiophenone hydrazone was obtained when the ketone was refluxed with a large excess of 50% hydrazone hydrate in methanol, forming a light yellow crystalline mass which slowly decomposed with deepening of colour. A small amount of the *azine* was also obtained as deep yellow prisms (from toluene), m. p. 214—215° (Found : N, 15·9. $C_{22}H_{30}N_4$ requires N, 16·0%).

The yellow oil left on evaporation of the collected mother-liquors from crystallisation of the ketone distilled at *ca.* 140°/20 mm. Its phenylhydrazone slowly crystallised and recrystallised from methanol in colourless prisms, m. p. 60·5°, not depressed in admixture with the phenylhydrazone of m. p. 60—65° recorded under (*a*). The oil was possibly *o*-dimethylaminopropiophenone and was redistilled (b. p. 245—250°/766 mm.; a pale green oil), but was still not pure (Found : C, 76·4; H, 8·4; N, 8·7%).

Orientation of p-*Dimethylaminopropiophenone.*—(i) *By a modified Wolff–Kishner reduction.* The ketone (4·78 g., 0·027 mole) was mixed with 96% hydrazine hydrate (7·5 c.c.) in redistilled ethylene glycol (100 c.c.) containing dissolved sodium (25 g.) and refluxed for 66 hours at 205—210° (metal-bath). The whole was poured into water, filtered, and extracted with ether. The extract was dried and evaporated, and the residual oil (2 g.) was distilled (b. p. 110—115°/13 mm.). Admixture with methyl iodide and storage at room temperature gave trimethyl-*p*-*n*-propylphenylammonium iodide, m. p. 185—187° (from ethanol). An authentic specimen, prepared from *N*-*n*-propylaniline (Hickinbottom, *J.*, 1930, 992), was rearranged to *p*-*n*-propylaniline, b. p. 220—222°, by anhydrous cobalt chloride (Cull, Davies, and Hulbert, *J. Soc. Chem. Ind.*, 1938, **349**), and methylated with methyl sulphate and aqueous sodium hydroxide, to give trimethyl-*p*-*n*-propylphenylammonium iodide, m. p. 191—192° (from ethanol).

(ii) *By lithium aluminium hydride reduction.* *p*-Dimethylaminopropiophenone (0·05 mole) in ether (500 c.c.) was added to a suspension of lithium aluminium hydride (0·03 mole) in ether (100 c.c.), and the whole stirred at 30° for 1 hour. Water and ammonium chloride solution were then added successively, and the separated ethereal solution was dried ($MgSO_4$). Removal of ether *in vacuo* at room temperature left a residual solid which was crystallised from light petroleum (b. p. 40—60°). A 55% yield of 1-*p*-dimethylaminophenylpropanol was obtained, of m. p. 46—47°, which was unaltered in admixture with a sample prepared according to Sachs and Sachs (*Ber.*, 1905, **38**, 514).

p-*Dimethylaminobutyrophenone.*—This *ketone* was obtained (37%) analogously from dimethylaniline and *n*-butyric acid, as colourless glistening platelets, m. p. 73—74°, not raised by further crystallisation from light petroleum (b. p. 60—80°) (Found : C, 75·5; H, 8·8; N, 7·3. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%).

The structure was established as above, by reduction with lithium aluminium hydride in ether to 1-*p*-dimethylaminophenylbutanol (61%), m. p. 38—40° not depressed on admixture with a sample (m. p. 37—39°) prepared from *n*-propylmagnesium bromide and *p*-dimethylaminobenzaldehyde (17% yield). The latter preparation was essentially that described by Sachs and Weigert (*Ber.*, 1907, **40**, 4362) but they did not obtain a pure product; theirs melted at 35°. Purification was achieved by keeping a light petroleum (b. p. 40—60°) solution at 5° for some hours (Found : C, 74·6; H, 10·1; N, 7·1. Calc. for $C_{12}H_{19}ON$: C, 74·6; H, 9·9; N, 7·3%).

p-*Dimethylaminovalerophenone.*—This ketone was obtained (28%) from dimethylaniline and *n*-valeric acid (Adams and Marvel, *J. Amer. Chem. Soc.*, 1920, **42**, 312). It consists of small glistening colourless crystals, m. p. 45—46° [from light petroleum (b. p. 40—60°)] (Found : C, 76·1; H, 9·5; N, 7·1. Calc. for $C_{13}H_{19}ON$: C, 76·1; H, 9·3; N, 6·8%).

p-*Diethylaminoacetophenone.*—This *ketone* was obtained (13—14%) from *p*-diethylaniline, acetic acid, and phosphoric oxide as colourless flat glistening needles, m. p. 47—48° (softening at 40°) (Found : C, 75·6; H, 9·0; N, 7·1. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%).

The author thanks Dr. A. J. Ewins, F.R.S., and Dr. R. Slack for their interest in this work, and the Directors of May & Baker Ltd. for permission to publish it. He also thanks Mr. W. G. Leeds, B.A., for some of the experimental work and Mr. S. Bance, B.Sc., for semimicroanalyses.

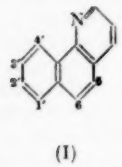
MAY AND BAKER LTD., DAGENHAM, ESSEX. [*Received, October 23rd*, 1951.]

116. *The Orientation of Some Substitution Products of 7 : 8-Benzoquinoline.*

By J. A. Barltrop and K. E. MacPhee.

Nitration of 7 : 8-benzoquinoline yields four mononitro-derivatives, the structures of three of which have been proved by comparison with synthetic specimens of known orientation. The nature of the fourth isomer is established by inference.

The mono-nitration of 7 : 8-benzoquinoline (I) has been investigated sporadically for half a century. Claus and Imhoff (*J. pr. Chem.*, 1898, **57**, 68) isolated two nitro-derivatives, m. p. 151° (nitrate, m. p. 178°) and m. p. 138° (nitrate, m. p. 173°), and suggested that these were 5- and 6-nitro-7 : 8-benzquinoline respectively. Haid (*Monatsh.*, 1906, **27**, 141), by a laborious fractionation, obtained four mononitro-7 : 8-benzoquinolines, m. p. 230°, 175°,



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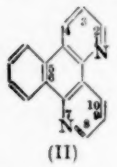
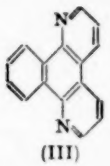


(II)



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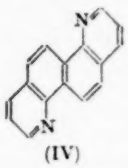

(IV)

166°, and 155°. He proved that the two most abundant isomers, of m. p. 230° and 175°, were substituted in the benzo-ring by reducing them to the corresponding amines and oxidising these to quinoline-7 : 8-dicarboxylic acid. Utermohlen and Hamilton (*J. Amer. Chem. Soc.*, 1941, **63**, 156), having performed a Skraup reaction on 4- and 5-nitro-1-naphthylamine, obtained 6- and 1′-nitro-7 : 8-benzoquinoline, m. p. 149° and 175° respectively, and suggested, without experimental evidence, that the latter was identical with Haid's isomer, m. p. 175°.

Data concerning the monoamino-7 : 8-benzoquinolines are rather more complete. I. G. Farbenind. (Fr. P. 796 601; *Chem. Abs.*, 1936, **30**, 6208) prepared 5-, 6-, 1′-, and 2′-amino-7 : 8-benzoquinoline from the corresponding 1-naphthylaminesulphonic acids by Skraup reactions followed by two-stage replacements of the sulphonic acid residues by amino-groups, and Schenkel and Schenkel (*Helv. Chim. Acta*, 1944, **27**, 1456) prepared 4′-amino-7 : 8-benzoquinoline by a similar method.

These data, collected in the table, lead to no certain conclusion as to the orientation of the nitration products of 7 : 8-benzoquinoline. The only apparent correlation is that between Haid's isomer, m. p. 175°, and 1′-nitro-7 : 8-benzoquinoline, but even this seems illusory since Haid reduced his product to an amine, m. p. 175°, whereas 1′-amino-7 : 8-benzoquinoline is reported to possess m. p. 192°.

In order to remove this obscurity, we set out to compare the four nitration products of (I) with synthetic specimens.

Ref.	M. p. of mononitro-isomers	M. p. of monoamino-isomers, from NO_2-compound	by Skraup reaction	Ref.
1	151°		5-NH_2, 146°	4
	138		6-NH_2, 118	
2	230	151° [a]	1′-NH_2, 192	
	175	175 [a]	2′-NH_2, ?	
	166		4′-NH_2, 85—86	5
	155			
3	6-NO_2, 149			
	1′-NO_2, 175			

Refs.: (1) Claus and Imhoff, (2) Haid, (3) Utermohlen and Hamilton, (4) I. G. Farbenind., (5) Schenkel and Schenkel, *locc. cit.*

[a] Ref. 2.

7 : 8-Benzoquinoline was nitrated according to Haid's directions (*loc. cit.*), but the isomers were separated by chromatography on alumina in ultra-violet light, the total yield of the mononitrobenzoquinolines being thus raised to 92%.

3-Nitro-1-naphthylamine (Hodgson, *J.*, 1943, 318) behaved anomalously under the conditions of the Skraup reaction: the only product isolated was 5 : 6-benzo-1 : 7-phenanthroline (II).

A Skraup reaction on 4-nitro-1-naphthylamine under the conditions described by Utermohlen and Hamilton (*loc. cit.*) and chromatographic analysis of the product gave 5 : 6-benzo-4 : 7-phenanthroline (III) and 6-nitro-7 : 8-benzoquinoline, m. p. 155°, identical with Haid's product of the same m. p. The ultra-violet absorption spectra of the two specimens also agree moderately well (see Fig. 1)—the deviations are probably caused by contamination of the synthetic compound by a minute amount of the phenanthroline (III). Reduction of the nitration product gave an amino-7 : 8-benzoquinoline, m. p. 117—118°. According to I. G. Farbenind. (*loc. cit.*), 6-amino-7 : 8-benzoquinoline has m. p. 118°.

FIG. 1.

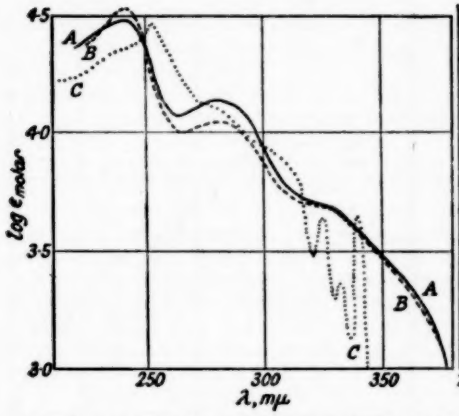

FIG. 2.

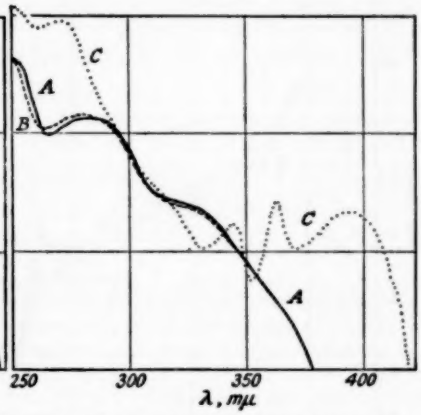

FIG. 1. *A, Nitration product, m. p.* 155°; *B, 6-nitro-7 : 8-benzoquinoline; C,* 5 : 6-*benzo-4 : 7-phenanthroline* (III). (*Solvent, methanol.*)

FIG. 2. *A, Nitration product, m. p.* 174°; *B, 1′-nitro-7 : 8-benzoquinoline; C, quinolino*(8′ : 7′-7 : 8)*quinoline* (IV). (*Solvent, methanol.*)

Utermohlen and Hamilton (*loc. cit.*) report the preparation of 1′-nitro-7 : 8-benzoquinoline from 5-nitro-1-naphthylamine by a Skraup reaction. We were unable to repeat their experiment, but, under modified conditions, obtained quinolino(8′ : 7′-7 : 8)quinoline (IV) and 1′-nitro-7 : 8-benzoquinoline, m. p. 174°. The latter was found to be identical with Haid's product, m. p. 174° by a mixed melting-point determination and by ultra-violet absorption spectra (Fig. 2). Reduction of the nitration product gave 1′-amino-7 : 8-benzoquinoline, m. p. 167—168° (Haid gives m. p. 175° and I. G. Farbenind. m. p. 192°).

2′-Nitro-7 : 8-benzoquinoline, synthesised from 6-nitro-1-naphthylamine, was found not to be identical with any of the nitration products; no fluorescent tetracyclic compound was formed with it.

For the synthesis of 3′-nitro-7 : 8-benzoquinoline, 8-nitro-2-naphthylamine (Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 636) was diazotised and converted into 1 : 7-dinitronaphthalene (Vesely and Dvorak, *Bull. Soc. chim.*, 1923, **33**, 319), then reduced to 7-nitro-1-naphthylamine, and subject to a Skraup reaction. 3′-Nitro-7 : 8-benzoquinoline, m. p. 224—225°, was isolated and found to be identical, by a mixed melting-point determination and ultra-violet spectra (Fig. 3), with Haid's main nitration product, m. p. 230°, which we find to possess m. p. 225°. Reduction gave 3′-amino-7 : 8-benzoquinoline, m. p. 146—147°.

In spite of repeated attempts, we were unable to isolate any 4'-nitro-7 : 8-benzoquinoline from the products of a Skraup reaction with 8-nitro-1-naphthylamine, although Schenkel and Schenkel (*loc. cit.*) were successful with the analogous 1-naphthylamine-8-sulphonic acid.

The structures of three of the four mono-nitration products of (I) have thus been established. Since it is extremely unlikely that the heterocyclic ring would be nitrated under the conditions used and since the fourth isomer (m. p. 166°) is not identical with 6-, 1'-, 2'-, or 3'-nitro-7 : 8-benzoquinoline described above (cf. Fig. 4), it follows that this substance must be either 5- or 4'-nitro-7 : 8-benzoquinoline. Furthermore, the isomer, m. p. 166°, on reduction, affords an amino-7 : 8-benzoquinoline of m. p. 140° and, since 4'-amino-7 : 8-benzoquinoline is reported to have m. p. 85—86° while the 5-amino-derivative has m. p. 146°, it follows that this fourth nitration product must be 5-nitro-7 : 8-benzoquinoline. Collateral evidence in support of this is provided (*a*) by the fact that phenanthrene, through steric hindrance, is resistant to substitution at $C_{(4)}$ which corresponds

FIG. 3. FIG. 4.

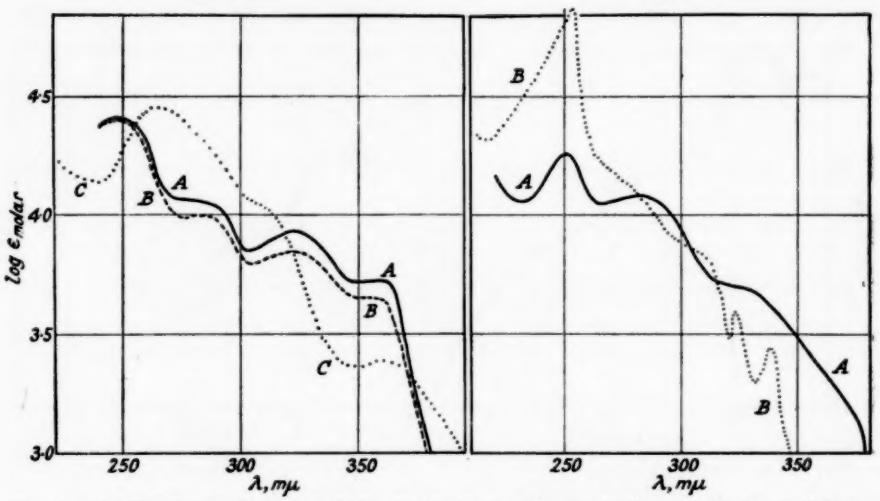

FIG. 3. *A, Nitration product, m. p. 225°; B, 2'-nitro-7 : 8-benzoquinoline; C, 3'-nitro-7 : 8-benzoquinoline.* (*Solvent, methanol.*)

FIG. 4. *A, Nitration product, m. p. 166°; B, 5 : 6-benzo-1 : 7-phenanthroline* (II). (*Solvent, methanol.*)

to $C_{(4')}$ in (I), and (*b*) by Longuet-Higgins and Coulson's calculations (*J.*, 1949, 971). These authors computed the electron density at the various carbon atoms of (I) and showed that the highest densities are located at $C_{(3')}$, $C_{(1')}$, $C_{(5)}$, and $C_{(6)}$ in this order of diminishing negative charge. Although it may be objected that the entity existing in the nitration mixture is the salt of (I), whereas the calculations of electron density are given only for the uncharged form of (I), nevertheless, the fact that we find that the nitration products of (I) in order of decreasing abundance are the 3'-, 1'-, and 6-nitro-7 : 8-benzoquinolines in agreement with the calculated order of decreasing electron density, justifies, we feel, our citing these calculations in support of the suggestion that the fourth isomer is 5-nitro-7 : 8-benzoquinoline.

EXPERIMENTAL

(M.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss and by Mr. F. C. Hall.)

7 : 8-*Benzoquinoline.*—A mixture of 1-naphthylamine (50 g.), glycerol (110 g.), concentrated sulphuric acid (200 g.), and arsenic pentoxide (50 g.) was heated at 140—150° for 4 hours and then poured into water (1 l.). Next morning, the solid (A) was collected and washed with water and sodium hydroxide solution. The filtrate was basified with concentrated sodium hydroxide

solution, and the precipitated tar collected and added to the solid (A), which was then boiled under reflux with benzene (400 c.c.) for 2 hours. The benzene extract, after being dried and distilled, gave 7 : 8-benzoquinoline (20 g.), b. p. 210—225°/47 mm., m. p. 51°.

Nitration of 7 : 8-*Benzoquinoline* (cf. Haid, *loc. cit.*).—7 : 8-Benzoquinoline (20 g.), dissolved in concentrated sulphuric acid (50 g.), was nitrated at 0—5° with a mixture of nitric acid (8 g.; *d* 1·5), and concentrated sulphuric acid (24 g.). After 1 hour, the mixture was poured into water (2 l.) and the precipitated nitro-7 : 8-benzoquinolines were collected, washed with water, dried, and extracted twice with boiling benzene (total vol., 2 l.). The benzene-insoluble material crystallised from ethanol in bright yellow needles (7 g.), m. p. 225° (Haid gives m. p. 230°). The benzene extract was chromatographed on four alumina columns (4 × 30 cm.) in parallel and the chromatogram developed with benzene in ultra-violet light until the lowest band had been washed through. The columns were then extruded and cut up in ultra-violet light, and the individual bands were extracted with hot ethanol. The benzene eluate and ethanol extracts, on concentration, yielded yellow solids, which on crystallisation from ethanol gave pure specimens of the isomeric nitro-7 : 8-benzoquinolines. Yields were: m. p. 225°, 11·6 g. (46·5%); m. p. 174°, 9·3 g. (37%); m. p. 166°, 0·6 g. (2·5%); m. p. 155°, 1·5 g. (6%); total yield, 23 g. (92%). Haid (*loc. cit.*) records m. p. 230°, 175°, 166°, 155°, and a total yield of 54%.

The product of m. p. 166°, which has not been orientated, behaves as a single substance when chromatographed on alumina; the 6- and the 1′-nitro-isomer are easily separated in this way. Further, a fusion diagram of the 6- and the 1′-nitro-isomer shows no sign of separation of a compound of m. p. 166°.

Attempted Preparation of 5-*Nitro*-7 : 8-*benzoquinoline*.—3-Nitro-1-naphthylamine (5 g.), glycerol (11 g.), concentrated sulphuric acid (20 g.), and arsenic pentoxide (5 g.) were heated together for 5 hours at 130—140°, poured into water (600 c.c.), heated to 100°, and filtered hot. The filtrate was basified with ammonia, and the green solid collected, washed with water, and dried. The solid, dissolved in benzene, was chromatographed on alumina. A yellow substance (0·9 g.), fluorescing blue in ultra-violet light, was isolated. Crystallisation from ethanol gave 5 : 6-*benzo*-1 : 7-*phenanthroline*, pale yellow needles, m. p. 163—164° (Found: C, 84.0; H, 4·6; N, 11·8. $C_{16}H_{10}N_2$ requires C, 83·5; H, 4·35; N, 12·15%).

6-*Nitro*-7 : 8-*benzoquinoline* (cf. Utermohlen and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 156).—Reaction of 4-nitro-1-naphthylamine (5 g.) as above and working up similarly gave a solid which was washed with water, dried, taken up in benzene, and chromatographed on alumina. 6-Nitro-7 : 8-benzoquinoline (0·3 g.), crystallised from ethanol, formed yellow needles, m. p. 155°, alone or when mixed with the nitration product, m. p. 155° (Found: C, 70·0; H, 3·5; N, 13·0. Calc. for $C_{13}H_8O_2N_2$: C, 69·6; H, 3·6; N, 12·5%). Utermohlen and Hamilton (*loc. cit.*) record m. p. 149°. Another product, apparently 5 : 6-benzo-4 : 7-phenanthroline, gave a blue fluorescence in ultra-violet light and crystallised from ethanol in pale yellow prisms, m. p. 159—160° (Found: C, 83·1; H, 4·4; N, 12·3%). Marckwald (*Annalen*, 1893, **274**, 365) reports m. p. 160°.

6-*Amino*-7 : 8-*benzoquinoline*.—The nitration product, m. p. 155° (0·3 g.), dissolved in hot acetic acid (20 c.c.), was treated with a hot solution of stannous chloride dihydrate (1·2 g.) in concentrated hydrochloric acid (2·5 c.c.). The solution became orange and, on its cooling, a solid separated, which was collected, triturated with concentrated sodium hydroxide solution, collected again, washed with water, and dried. Crystallisation from ethanol gave 6-amino-7 : 8-benzoquinoline as light brown platelets, m. p. 117—118° (Found: C, 79·9; H, 5·1; N, 14·4%). I. G. Farbenind. (*loc. cit.*) give m. p. 118°.

1′-*Nitro*-7 : 8-*benzoquinoline*.—5-Nitro-1-naphthylamine (5 g.) gave, by a Skraup reaction as above, a product which was extracted with hot ethanol (2 × 300 c.c.). The extract was concentrated to small volume, diluted with water (200 c.c.), and basified with ammonia. The precipitated solid was collected, washed with water, and dried. The combined solids were extracted with benzene and chromatographed on alumina. 1′-Nitro-7 : 8-benzoquinoline (0·3 g.) was obtained as a yellow solid, which crystallised from ethanol in pale yellow needles, m. p. 174° alone or mixed with a specimen of the nitration product, m. p. 174° (Found: C, 69·6; H, 3·8; N, 12·2%). Utermohlen and Hamilton (*loc. cit.*) give m. p. 175°. Another product (0·3 g.), which gave a blue fluorescence in ultra-violet light and appears to be quinolino-(8′ : 7′ : 7 : 8) quinoline, crystallised from ethanol in bright yellow needles, m. p. 216° (Found: C, 83·0; H, 4·4; N, 12·0. Calc. for $C_{16}H_{10}N_2$: C, 83·5; H, 4·35; N, 12·15%). Finger and Spitz (*J. pr. Chem.*, 1909, **79**, 445) give m. p. 217°.

1′-*Amino*-7 : 8-*benzoquinoline*.—The nitration product, m. p. 174°, when reduced in the same manner as 6-nitro-7 : 8-benzoquinoline gave 1′-amino-7 : 8-benzoquinoline, which crystallised

from ethanol in pale yellow platelets, m. p. 167—168° (Found: C, 79·9; H, 5·2; N, 14·7%). Haid (*loc. cit.*) gives m. p. 175° and I. G. Farbenind. (*loc. cit.*) give m. p. 192°. *1'-Acetamido-7 : 8-benzoquinoline* separated from ethanol in needles, m. p. 205° (Found: C, 75·9; H, 5·1; N, 11·6. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%).

2'-Nitro-7 : 8-benzoquinoline.—A Skraup reaction, as above, with 6-nitro-1-naphthylamine (5 g.) gave, after chromatography, *2'-nitro-7 : 8-benzoquinoline* (0·4 g.), which crystallised from ethanol in pale yellow needles, m. p. 200—201° (Found: C, 69·2; H, 3·4; N, 12·2%).

3'-Nitro-7 : 8-benzoquinoline.—7-Nitro-1-naphthylamine (4·1 g.) similarly gave *3'-nitro-7 : 8-benzoquinoline* (0·3 g.) as fluffy, yellow needles (from ethanol), m. p. 224—225° alone or mixed with a specimen of the nitration product, m. p. 225° (Found: C, 69·9; H, 3·9; N, 12·4%).

3'-Amino-7 : 8-benzoquinoline.—The above compound was reduced in the same manner as 6-nitro-7 : 8-benzoquinoline. The aminobenzoquinoline crystallised from ethanol in light brown platelets, m. p. 146—147° (Found: C, 80·2; H, 5·3; N, 14·4%). Haid gives m. p. 151° for the amine derived by reducing the nitration product, m. p. 225°. *3'-Acetamido-7 : 8-benzoquinoline* crystallised from ethanol in pale pink needles, m. p. 183° (Found: C, 75·8; H, 5·2; N, 11·9%).

Attempted Preparation of 4'-Nitro-7 : 8-benzoquinoline.—8-Nitro-1-naphthylamine (Morgan and Jones, *J. Soc. Chem. Ind.*, 1923, **42**, 341T) (5 g.) was subjected to a Skraup reaction under the conditions recorded above but only traces of starting material could be isolated. Variations in the reaction conditions brought no success.

Reduction of Nitration Product of M. p. 166°.—The substance was reduced under the conditions described above. *x*-Amino-7 : 8-benzoquinoline crystallised from ethanol in orange needles, m. p. 140° (decomp.). The *acetyl* derivative separated from ethanol in pale yellow needles, m. p. 194—195° (Found: C, 75·8; H, 4·9; N, 12·3%).

We are grateful to Dr. F. Strauss for determining the ultra-violet absorption spectra.

Dyson Perrins Laboratory, Oxford. [*Received, August 23rd,* 1951.]

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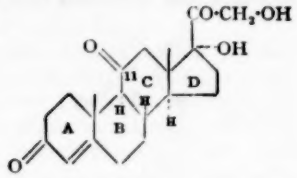
117. *Studies of the Diels–Alder Reaction. Part I. The Reaction between 1-Vinylcyclohex-1-ene and Benzoquinone, and the Reduction of $\Delta^{2:9(14)}$-Decahydro-1 : 4-diketophenanthrene.*

By P. A. Robins and James Walker.

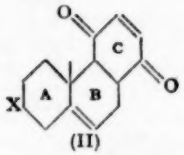
The Diels–Alder reaction between 1-vinyl*cyclo*hex-1-ene and benzoquinone afforded the highly characteristic $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (V), and the reduction of (V) under a variety of conditions has been studied. Reduction with zinc and acetic acid under mild conditions gave $\Delta^{9(14)}$-dodecahydro-1 : 4-diketophenanthrene (VIII), and catalytic hydrogenation under progressively vigorous conditions gave perhydro-1 : 4-diketophenanthrene (XII), perhydro-4-hydroxy-1-ketophenanthrene (XIII), and perhydro-1 : 4-dihydroxyphenanthrene (XVI). These reactions are discussed in the light of the stereochemical factors involved.

Methods for the construction of the tetracyclic steroid nucleus from hydro-1-ketophenanthrene derivatives are now well known and their application to hydro-1-ketophenanthrenes suitably substituted in the 4-position could be made the basis for the synthesis of cortisone (I) and similar compounds having a substituent in the 11-position (steroid enumeration). Such compounds are to be found in the decahydro-1 : 4-diketophenanthrenes (II), which should be available as the products of Diels–Alder reactions between suitably substituted vinyl*cyclo*hexenes (III) and benzoquinone, and the stereochemical problems involved are not such as might prove to be insuperable. The stereochemistry of the sterol system is now well understood and the predictable stereochemical course of the Diels–Alder reaction enables one to assign configurations to adducts, such as (II), with some degree of confidence. Furthermore, the presence of carbonyl groups adjacent to asymmetric centres permits selective inversions to be effected at appropriate stages in order to relate the configurations of the synthetic materials to those of the natural products.

We have commenced a study of this problem by undertaking an examination of the Diels–Alder reaction between vinyl*cyclo*hexene and benzoquinone, together with an examination of the controlled reduction of the resulting product. The reaction between



(I)



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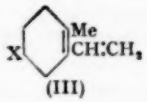
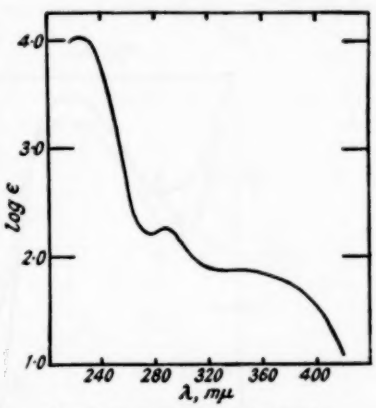


(III)

vinyl*cyclo*hexene and benzoquinone, to give $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (IV), has been recorded by Cook and Lawrence (*J.*, 1938, 58) and by Backer and van der Bij (*Rec. Trav. chim.*, 1943, **62**, 561), and Grob, Jundt, and Wicki (*Helv. Chim. Acta*, 1949, **32**, 2427) used this substance (IV) to gain access to 1 : 4-dimethoxyphenanthrene. No stereochemical considerations have, however, been mentioned nor has any study of the reduction of (IV) been carried out hitherto. It has been found extremely difficult to obtain really pure specimens of 1-vinyl*cyclo*hexene, and the use of greater amounts than *ca.* 0·6 molecular proportion of benzoquinone in the Diels–Alder reaction has resulted in the presence of unchanged quinone in the product. The difficulties are doubtless attributable to lack of marked discontinuity in the rate of hydrogenation of 1-ethynyl*cyclo*hexanol, with the result that the intermediate 1-vinyl*cyclo*hexanol may be contaminated with some 1-ethyl*cyclo*hexanol, and to the possibility of unchanged 1-vinyl*cyclo*hexanol co-distilling with the hydrocarbon in the subsequent preparation of 1-vinyl*cyclo*hexene. The product (IV), however, is an extremely characteristic substance, although it is notable for its extreme lability in the presence of traces of alkali. The light absorption of (IV) (Fig. 1), containing the interesting –CO·CH:CH·CO– chromophore, appeared to be intermediate between that of the quinone adduct of lævopimaric acid and that of diacetylethylene as recorded by Ruzicka and Kaufmann (*Helv. Chim. Acta*, 1941, **24**, 1425).

FIG. 1.

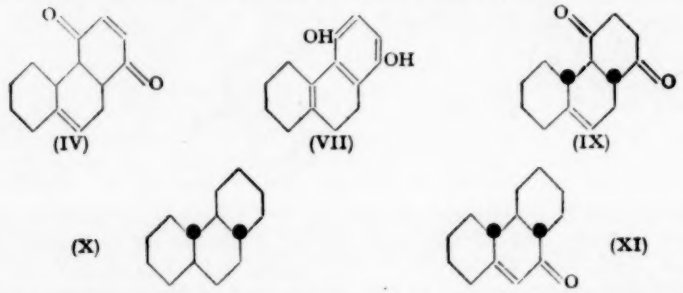


$\Delta^{2:9(14)}$-*Decahydro*-1 : 4-*diketophenanthrene* (IV).

From the so-called Alder rules (Alder and Stein, *Angew. Chem.*, 1937, **50**, 510; cf. Bergmann and Eschinazi, *J. Amer. Chem. Soc.*, 1943, **65**, 1405) one can assign to (IV) the *syn-cis*-configuration (V) (see p. 645), in which the dots indicate that hydrogen atoms so denoted are on the side of the carbon skeleton nearer to the reader (cf. Linstead, *Chem. and Ind.*, 1937, **56**, 510; Linstead and Walpole, *J.*, 1939, 842). The substance (V) was readily aromatised to 5 : 6 : 7 : 8 : 10 : 13-hexahydro-1 : 4-dihydroxyphenanthrene (VI) by treatment either with alkali or with acid (cf. Grob *et al.*, *loc. cit.*), and the close correspondence between the light absorption of (VI) and that of quinol (Fig. 2) indicates that the remaining isolated double bond had not moved into the 13 : 14-position into conjugation with the aromatic ring to give (VII).

Treatment of (V) with zinc powder and acetic acid at room temperature effected reduction at the 2 : 3-double bond to give $\Delta^{9(14)}$-dodecahydro-1 : 4-diketophenanthrene in excellent yield, and there is no reason to believe, considering the mildness of the conditions used, that this substance is other than the *syn-cis*-compound (VIII). On the other hand, reduction with zinc in hot acetic acid gave either a stereoisomeric $\Delta^{9(14)}$-dodecahydro-1 : 4-diketophenanthrene, in which inversion at either $C_{(11)}$ or at $C_{(12)}$ had taken place,

or the isomeric Δ^{13}-dodecahydrodiketophenanthrene. In the event of this substance's being a stereoisomeride of (VIII), it is unlikely that inversion at both $C_{(11)}$ and $C_{(12)}$ would have taken place to give the *anti-cis*-compound, with *cis*-fusion of rings B and C, but it is distinctly probable that equilibration of (VIII) would give the *anti-trans*-compound



(IX), in line with the greatest stability of the *trans-anti-trans*-form (X) among perhydrophenanthrenes (cf. Johnson, *Experientia*, 1951, **8**, 315), and the fact that the addition product of sodio*cyclo*hexanone to acetyl*cyclo*hexene is the *anti-trans*-compound (XI) (Linstead, Davis, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 2009). Further reduction of (VIII) by catalytic hydrogenation in the presence of palladised strontium carbonate

FIG. 2.

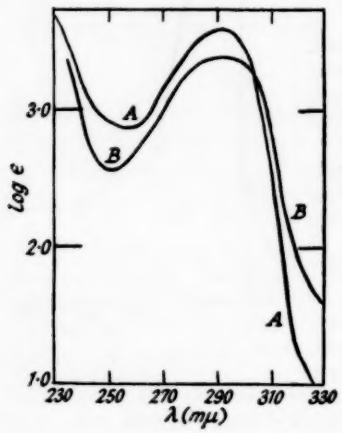


FIG. 3.

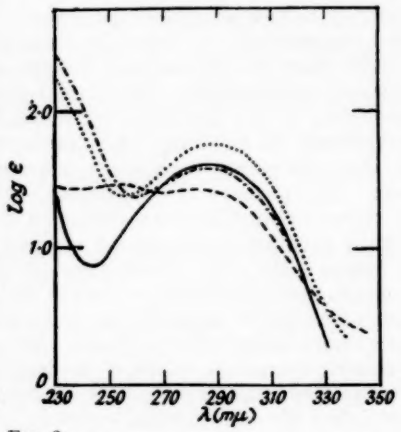


FIG. 2.

A 5 : 6 : 7 : 8 : 10 : 13-*Hexahydro*-1 : 4-*dihydroxyphenanthrene* (VI).
B *Quinol.*

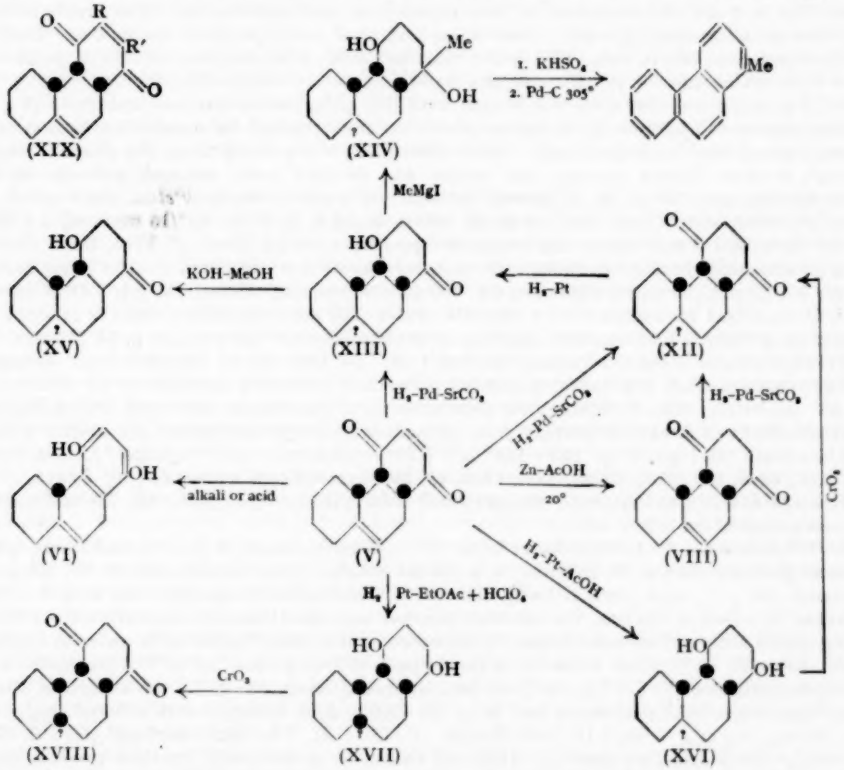
FIG. 3.

—·—·—·— $\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*diketophenanthrene* (VIII).
———— *Perhydro*-1 : 4-*diketophenanthrene* (XII).
– – – – – – – – *Perhydro*-4-*hydroxy*-1-*ketophenanthrene* (XIII).
. . . . . *Compound* (IX).

afforded perhydro-1 : 4-diketophenanthrene (XII), and the same compound was obtainable by direct hydrogenation of (V). In (XII) the stereochemical configuration at $C_{(14)}$ is not readily predictable, but provisionally (XII) may be assigned the *trans-syn-cis*-configuration, by analogy with the hydrogenation of (XI) to the *trans-anti-trans*-perhydro-9-ketophenanthrene (Linstead *et al.*, *loc. cit.*). This provisional assignment of the configuration of (XII) would imply that ring C does not interfere with the hydrogenation of the 9(14)-double bond in (VIII) to any appreciable extent by catalyst hindrance (cf. Linstead *et al.*, *ibid.*, p. 1985). In addition to being produced in hydrogenations with a palladium

catalyst in neutral solution, (XII) was also obtained from diol A (see below), obtained by complete hydrogenation of (V) with Adams's platinum oxide catalyst in acidic media, indicating the same stereochemical course for the hydrogenation of the 9(14)-double bond under both sets of conditions. Light-absorption data for these ketonic compounds are collected in Fig. 3.

Further hydrogenation of (XII) with Adams's platinum oxide catalyst afforded a keto-alcohol (XIII), and the same compound, surprisingly, was also obtained from (V) directly by prolonged hydrogenation in the presence of palladised strontium carbonate. The constitution of (XIII) followed from the fact that treatment with methylmagnesium iodide, dehydration of the resulting perhydro-1 : 4-dihydroxy-1-methylphenanthrene (XIV), and dehydrogenation with palladised charcoal afforded 1-methylphenanthrene. The *cis*-configuration of (XIII) at the B–C ring fusion followed from the fact that, being a derivative of *cis*-α-decalone, it was readily converted into a stereoisomeride (XV) by treatment with 1% methanolic alkali. Exhaustive hydrogenation of (V) in the presence of Adams's catalyst in acetic acid solution gave a perhydro-1 : 4-dihydroxyphenanthrene (diol A), which was isolated by way of its dibenzoate and subsequent hydrolysis. The yields of the dibenzoate were variable but the rate of hydrogenation was greatly accelerated by the addition of a small proportion of perchloric acid (cf. Hershberg *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1144). On oxidation with chromic acid, this diol (diol A) afforded



the perhydro-1 : 4-diketophenanthrene (XII), which we had already obtained directly from (V) and also from (VIII); diol A is therefore assigned configuration (XVI). In ethyl acetate containing a small proportion of perchloric acid, however, hydrogenation of (V) afforded, in addition to (XVI), a second crystalline perhydro-1 : 4-dihydroxyphenanthrene (diol B), giving rise on oxidation with chromic acid to a perhydro-1 : 4-diketo-

phenanthrene stereoisomeric with (XII); the stereochemical differences between diol A and diol B and the two derived ketones are probably associated with $C_{(14)}$, rather than with $C_{(11)}$ or $C_{(12)}$, and diol B is therefore provisionally assigned configuration (XVII) and the derived diketone is assigned configuration (XVIII).

The Diels–Alder reaction between 1-vinyl*cyclo*hex-1-ene and toluquinone gave a mixture of products (XIX; R = H, R′ = Me) and (XIX; R = Me, R′ = H) which could only be separated with difficulty.

Experimental

1-*Ethynyl*cyclo*hexanol*.—Redistilled *cyclo*hexanone (196 g., 2·0 g.-mol.) in dry ether (400 c.c.) was added during 45 minutes to a stirred suspension of sodium acetylide [prepared from 92 g. of sodium (4 g.-atoms) by the method of Heilbron, Jones, and Weedon (*J.*, 1945, 83)] in liquid ammonia (*ca.* 3·5 l.), contained in a large Dewar vessel, through which a slow stream of gaseous acetylene was being passed. After 7 hours' stirring the mixture was kept overnight. Ammonium chloride (216 g., 4 g.-mol.) was then added in small portions with stirring, and the greater part of the ammonia allowed to evaporate. Much water was then added to the semi-solid mass, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted three times with ether. The combined organic layers were washed with 2N-sulphuric acid until free from ammonia, dried (Na_2SO_4), and fractionated twice, giving ethynyl*cyclo*hexanol (186 g.), b. p. 74—78°/18 mm., n_D^{20} 1·4859; a small fore-run containing a trace of *cyclo*hexanone was rejected in each distillation. The product slowly solidified to a low-melting solid. *Inter alios*, Campbell *et al.* (*J. Amer. Chem. Soc.*, 1938, **60**, 2882) record b. p. 74°/14 mm., n_D^{20} 1·4820; Chanley (*ibid.*, 1948, **70**, 244) records m. p. 28—30°.

1-*Vinyl*cyclo*hexanol*.—(a) *By catalytic hydrogenation.* 1-Ethynyl*cyclo*hexanol (62 g., 0·5 g.-mol.) in methanol (200 c.c.) was stirred with 2% palladised strontium carbonate (6 g.) in an atmosphere of hydrogen until the calculated volume required for semihydrogenation of the ethynyl group had been absorbed. After removal of the solvent from the filtered solution through a short Dufton column, the residue was distilled under reduced pressure, to give 1-vinyl*cyclo*hexanol (50 g.), b. p. 66—68°/14 mm., n_D^{20} 1·4798. Nazarov *et al.* (*Bull. Acad. Sci. U.S.S.R.*, 1946, 305; *Chem. Abs.*, 1949, **43**, 6969) record b. p. 67·5—68°/15 mm., n_D^{20} 1·4740.

(b) *By reduction with sodium and ethanol in liquid ammonia* (cf. Birch, *J.*, 1945, 809). Sodium (25·5 g.) was added in small portions with vigorous stirring to a solution of 1-ethynyl*cyclo*hexanol (62 g., 0·5 g.-mol.) in liquid ammonia (*ca.* 500 c.c.) containing ethanol (51 g.). After most of the ammonia had been allowed to evaporate, water (250 c.c.) was added and the product was recovered in ether. Fractionation afforded 1-vinyl*cyclo*hexanol (27·6 g.), b. p. 76°/17 mm.

1-*Vinyl*cyclo*hex*-1-*ene*.—1-Vinyl*cyclo*hexanol (61 g.) was slowly distilled in a stream of nitrogen from a flask containing powdered potassium hydrogen sulphate (5 g.) and heated at 150° (oil-bath). The distillate, after separation from the aqueous layer and drying (K_2CO_3), was redistilled in a stream of nitrogen from potassium hydrogen sulphate (1 g.), to give 1-vinyl-*cyclo*hex-1-ene (46·1 g.), b. p. 143—144°, n_D^{19} 1·4950. Nazarov and Nagibina (*J. Gen. Chem. U.S.S.R.*, 1948, **18**, 1090; *Chem. Abs.*, 1949, **43**, 1333) record b. p. 142—144°, n_D^{19} 1·4915.

Benzoquinone.—Benzoquinone was prepared from quinol (*Org. Synth.*, **16**, 73) and purified by steam-distillation before use.

$\Delta^{2:9(14)}$-*Decahydro*-1 : 4-*diketophenanthrene* (V).—Benzoquinone (6 g., 0·6 mol.) was added in small portions during 30 minutes to a stirred solution of 1-vinyl*cyclo*hex-1-ene (10 g.) in methanol (50 c.c.), each portion being allowed to dissolve before another was added. After a further 30 minutes' stirring, the reaction mixture was left at room temperature for 4 hours, during which a crystalline solid began to separate; it was then diluted with water (5 c.c.) and cooled to −5°. Filtration afforded massive pale yellow prisms of $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (V) (10·7 g., 88% on benzoquinone), m. p. 85—87°. An analytical sample crystallised from light petroleum had m. p. 87—88°; light absorption in ethanol, $\lambda_{max.}$ 225, 290, 340 mμ, log $\varepsilon_{max.}$ 4·08, 2·15, 1·90 (Found: C, 77·7; H, 7·3. Calc. for $C_{14}H_{16}O_2$: C, 77·7; H, 7·5%). Cook and Lawrence (*J.*, 1938, 58) record m. p. 84—84·5° for their product which was crystallised from methanol: this observation was confirmed by Backer and van der Bij (*Rec. Trav. chim.*, 1943, **62**, 571), who also state that crystallisation from light petroleum gave needles, m. p. 136—137°. Although we have used light petroleum exclusively as a solvent we have not encountered material of this higher m. p.

The compound was very sensitive to alkali, and decomposed slowly if stored in a soda-glass container; it was best stored in the dark in a Pyrex flask. The use of a full molecular

proportion of benzoquinone did not improve the yield and caused difficulty by crystallisation of the quinone from the reaction mixture with the product. Variation in the method of preparation of the 1-vinyl*cyclo*hexanol (see above) did not affect the final yield of decahydrodiketophenanthrene from 1-vinyl*cyclo*hex-1-ene.

5 : 6 : 7 : 8 : 10 : 13-*Hexahydro*-1 : 4-*dihydroxyphenanthrene* (VI).—(*a*) A solution of $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (200 mg.) in methanol (50 c.c.) was treated with 2N-aqueous sodium hydroxide (3 c.c.). After the reactants had been mixed by swirling, during which a darkening in colour took place, 2N-hydrochloric acid (10 c.c.) was added, and the mixture was diluted with water and extracted with ether. The ethereal extract, after being washed with water and dried (Na_2SO_4), afforded, on evaporation, 5 : 6 : 7 : 8 : 10 : 13-hexahydro-1 : 4-dihydroxyphenanthrene (VI) (150 mg.), which separated from benzene–light petroleum in stout needles, m. p. 175—177°; light absorption in ethanol, $\lambda_{max.}$ 292 mμ, log $\varepsilon_{max.}$ 3·6. Grob *et al.* (*Helv. Chim. Acta*, 1949, **32**, 2427) record m. p. 175—177°. The substance was soluble in aqueous alkali, giving a solution that darkened rapidly in air.

(*b*) A solution of the decahydrodiketophenanthrene (V) (200 mg.) in methanol (10 c.c.) was boiled under reflux with concentrated hydrochloric acid (0·5 c.c.). The product was isolated by cooling, dilution with water, and extraction with ether. Crystallisation from benzene–light petroleum gave a product (VI) identical with that obtained in (*a*).

$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*diketophenanthrene* (VIII).—$\Delta^{2:9(14)}$-Decahydro-1 : 4-diketophenanthrene (1 g.) was dissolved in glacial acetic acid (50 c.c.), and zinc powder (1 g.) was added to the stirred solution at room temperature. After 5 minutes' stirring the unchanged zinc was filtered off and washed with a little ether, and the combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was extracted with boiling light petroleum, which, after filtration and cooling, deposited clusters of small, colourless prisms (0·84 g.) of ***$\Delta^{9(14)}$-dodecahydro*-1 : 4-*diketophenanthrene*** (VIII), m. p. 81—82; light absorption in ethanol, $\lambda_{max.}$ 286 mμ, log $\varepsilon_{max.}$ 1·58 (Found : C, 77·0; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). The *bis*-2 : 4-*dinitrophenylhydrazone* separated from methanol–ethyl acetate as an amorphous yellow powder, which sintered and decomposed above 145° (Found : N, 19·3. $C_{26}H_{26}O_8N_8$ requires N, 19·4%).

Reduction of $\Delta^{2:9(14)}$-Decahydro*-1 : 4-*diketophenanthrene (V) ***with Zinc in Boiling Acetic Acid.***—A solution of the diketone (1 g.) in glacial acetic acid (60 c.c.) was boiled under reflux with zinc powder (3·6 g.) for 4 hours. After cooling, zinc acetate and unused zinc were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was extracted with boiling light petroleum and, on cooling, the extract deposited rosettes of fine needles (300 mg.). A further crystallisation from light petroleum gave a *compound* (?IX), m. p. 138—139°, which gave a pale yellow colour with tetranitromethane; light absorption in ethanol, $\lambda_{max.}$ 289 mμ, log $\varepsilon_{max.}$ 1·76 (Found : C, 77·1; H, 8·3. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). The *bis*-2 : 4-*dinitrophenylhydrazone* separated from toluene as a yellow amorphous powder, m. p. 242—243° (decomp.) (Found : N, 18·9. $C_{26}H_{26}O_8N_8$ requires N, 19·4%).

Perhydro*-1 : 4-*diketophenanthrene (XII).—(*a*) $\Delta^{2:9(14)}$-Decahydro-1 : 4-diketophenanthrene (V) (5 g.) in methanol (150 c.c.) was shaken with 2% palladised strontium carbonate (2 g.) in hydrogen at room temperature and pressure until 2 molecular proportions of hydrogen had been absorbed (about 3 hours). After filtration and removal of the solvent the residue, crystallised from aqueous methanol, afforded colourless needles (3·05 g.) of perhydro-1 : 4-diketophenanthrene (XII), m. p. 107—109° alone and in admixture with the product obtained by oxidation of diol A (see below). Substitution of a platinum oxide catalyst in this hydrogenation gave a gummy product that could not be crystallised.

(*b*) A solution of $\Delta^{9(14)}$-dodecahydro-1 : 4-diketophenanthrene (VIII) (500 mg.) in ethyl acetate (40 c.c.) was shaken in hydrogen with Adams's platinum oxide catalyst (50 mg.) until 1 molecular proportion of hydrogen had been absorbed. After removal of the catalyst and evaporation of the solvent, crystallisation of the residue from light petroleum gave perhydro-1 : 4-diketophenanthrene (XII) (0·34 g.), m. p. 108—109°, alone and in admixture with specimens obtained by alternative routes.

Perhydro*-4-*hydroxy*-1-*ketophenanthrene (XIII).—(*a*) A solution of $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (V) (500 mg.) in methanol (20 c.c.) was shaken with 2% palladised strontium carbonate (0·5 g.) in hydrogen at room pressure and temperature for 24 hours; 2·6 molecular proportions of hydrogen had then been absorbed and the rate of uptake had become negligible. After removal of the catalyst and evaporation of the solvent, the residue crystallised. Recrystallisation from a large volume of light petroleum or, preferably, ligroin, gave felted needles (350 mg.) of ***perhydro*-4-*hydroxy*-1-*ketophenanthrene*** (XIII), m. p. 136—138°; light absorption

in ethanol, $\lambda_{max.}$ 254, 282 mμ, log $\varepsilon_{max.}$ 1·46, 1·43 (Found: C, 75·7, 75·8, 75·3; H, 9·8, 9·6, 10·1. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%). The 2 : 4-*dinitrophenylhydrazone* separated from benzene in small orange needles, m. p. 219—221° (Found: N, 14·5. $C_{20}H_{26}O_5N_4$ requires N, 14·0%). The *acetate* crystallised from light petroleum at −5° in flattened needles, m. p. 79—80° (Found: C, 72·5; H, 9·4. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·2%).

(*b*) A solution of perhydro-1 : 4-diketophenanthrene (XII) (4·0 g.) in methanol (100 c.c.) was shaken in hydrogen at room pressure and temperature with Adams's platinum oxide catalyst (200 mg.) for 4 hours, 0·86 molecular proportion of hydrogen being absorbed. Isolation of the product in the usual way and crystallisation from ligroin (250 c.c.) afforded felted needles (3·0 g.) of perhydro-4-hydroxy-1-ketophenanthrene (XIII), m. p. 138—139° alone and in admixture with the product obtained in (*a*) above.

Perhydro-4-hydroxy-1-ketophenanthrene (XV).—A solution of perhydro-4-hydroxy-1-ketophenanthrene (XIII) (200 mg.) in 1% methanolic potassium hydroxide (20 c.c.) was boiled under reflux for 30 minutes. The product was isolated by dilution with water, and crystallisation from ligroin gave needles (150 mg.) of the stereoisomeric *perhydro-4-hydroxy-1-ketophenanthrene* (XV), m. p. 141—142°, depressed to 105—110° on admixture with the starting material (Found: C, 75·3; H, 9·8. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

Perhydro-1 : 4-dihydroxyphenanthrene.—(*a*) A solution of $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (500 mg.) in glacial acetic acid (30 c.c.) was shaken in hydrogen at room pressure and temperature with Adams's platinum oxide catalyst (50 mg.) until 4 molecular proportions of hydrogen had been absorbed; about 72 hours were required and a fresh portion of catalyst was added after 48 hours. The gum obtained by removal of the catalyst and evaporation of the solvent was treated with benzoyl chloride in pyridine overnight at room temperature. Isolation of the neutral material with ether gave a gum, which, on dissolution in a small volume of methanol, deposited massive prisms of 1 : 4-*dibenzoyloxyperhydrophenanthrene* (diol A dibenzoate) (450 mg., 45%), m. p. 130—134°. A specimen, recrystallised from ethyl acetate, had m. p. 134—135° (Found: C, 77·9; H, 7·4. $C_{28}H_{32}O_4$ requires C, 77·8; H, 7·5%). The rate of hydrogenation could be greatly increased by the addition of a small quantity of 72% perchloric acid (cf. Hershberg *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1144), but the yields of diol A dibenzoate varied.

Hydrolysis of this dibenzoate by refluxing it with excess of 5% methanolic potassium hydroxide for 30 minutes gave *perhydro-1 : 4-dihydroxyphenanthrene* (XVI) (diol A), which separated from light petroleum containing a little ethyl acetate in prisms, m. p. 134—135°, depressed to 110—115° on admixture with the dibenzoate (above) of the same m. p. (Found: C, 75·0; H, 10·6. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%).

Oxidation of the diol with chromium trioxide (2·2 mols.) in glacial acetic acid at room temperature overnight gave *perhydro-1 : 4-diketophenanthrene* (XII), which separated from light petroleum in clusters of needles, m. p. 108·5—110°; light absorption in ethanol, $\lambda_{max.}$ 285 mμ, log $\varepsilon_{max.}$ 1·62 (Found: C, 76·3; H, 9·5. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%). The *bis*-2 : 4-*dinitrophenylhydrazone* separated from methoxyethanol as a brick-red powder, which sintered and decomposed above 165° (Found: N, 18·9. $C_{26}H_{28}O_8N_8$ requires N, 19·3%).

(*b*) A solution of $\Delta^{2:9(14)}$-decahydro-1 : 4-diketophenanthrene (1·0 g.) in ethyl acetate (100 c.c.), containing perchloric acid (0·1 c.c. of 70%), was shaken in hydrogen at room pressure and temperature with Adams's platinum oxide catalyst (100 mg.) until absorption of hydrogen ceased, four molecular proportions being absorbed in 3½ hours. After removal of the catalyst, the ethyl acetate solution was washed with aqueous sodium hydrogen carbonate to remove perchloric acid and then concentrated (to *ca.* 10 c.c.). Addition of an equal volume of light petroleum gave a white solid (160 mg.), which, on crystallisation from benzene–ethanol, gave fine needles of a stereoisomeric *perhydro-1 : 4-dihydroxyphenanthrene* (XVII) (diol B), m. p. 212° (Found: C, 75·5; H, 10·9. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%). Diol B, on oxidation with chromium trioxide (2·2 mols.) in glacial acetic acid, gave a stereoisomeric *perhydro-1 : 4-diketophenanthrene* (XVIII), crystallising from light petroleum in fine needles, m. p. 115—116°, depressed on admixture with the perhydro-diketone (XII), m. p. 108·5—110°, from diol A (Found: C, 76·6; H, 9·5. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%).

The remainder of the hydrogenation product, after separation of diol B, was isolated by evaporation of the solvent. The resultant gum, after treatment with benzoyl chloride and pyridine in the usual way, followed by recovery of the neutral fraction in ether, afforded the dibenzoate (220 mg.) of diol A.

Perhydro-1 : 4-dihydroxy-1-methylphenanthrene (XIV).—The keto-alcohol (XIII) (2·0 g.) in

dry benzene (60 c.c.) was added to a stirred, boiling solution of methylmagnesium iodide (from 2·5 g. of magnesium and 14·5 g. of methyl iodide) in benzene (100 c.c.). After being stirred under reflux for 3½ hours, the reaction mixture was cooled to 0° and decomposed with ice-cold 4N-sulphuric acid (50 c.c.). After separation of the benzene layer, the aqueous phase was extracted once with ether, and the combined organic layers were washed successively with 2N-sulphuric acid, water, and saturated aqueous sodium hydrogen carbonate. Removal of the solvent left a gum (2·08 g.), which appeared, from its behaviour with Brady's reagent, still to contain a trace of ketonic material. The gum was dissolved in ethanol (90 c.c.) and glacial acetic acid (10 c.c.) and refluxed with Girard's reagent P (5 g.) for 30 minutes. After cooling and pouring into water containing 2N-sodium hydroxide (75 c.c.; 90% of that required for neutralisation of the acetic acid), the non-ketonic fraction was recovered in ether. Evaporation of the dried ethereal solution gave a gum (1·89 g.), which solidified on trituration with light petroleum to give *perhydro*-1 : 4-*dihydroxy*-1-*methylphenanthrene* (1·40 g.), m. p. 115—121°. Crystallisation from light petroleum afforded colourless prisms, m. p. 123°, giving no colour with tetranitromethane (Found: C, 75·4; H, 10·7. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%).

Dehydration and Dehydrogenation of (XIV) *to* 1-*Methylphenanthrene.*—Crude perhydro-1 : 4-dihydroxy-1-methylphenanthrene (1·3 g.) and potassium hydrogen sulphate (2·5 g.) were heated in an atmosphere of nitrogen to 180° for 30 minutes. After cooling and addition of water, the organic material was isolated with ether. The dried ethereal solution was evaporated, and the oily residue, taken up in low-boiling light petroleum, was allowed to run through a short column of activated alumina (Peter Spence & Sons Ltd., Type H). The eluate, on distillation, yielded an oily residue (0·7 g.), giving a deep brown colour with tetranitromethane. The oil was heated at 300—310° (metal-bath) with palladised charcoal (1·0 g., containing 10% of palladium) in diphenylamine under reflux in a slow stream of carbon dioxide. The effluent gases were collected in a graduated receiver over 40% aqueous potassium hydroxide. After 5 hours' heating, no further evolution of hydrogen took place (total vol., 260 c.c.; calc. for a decahydromethylphenanthrene, 390 c.c.). The mixture was cooled, taken up in ether, and filtered, and the filtrate was saturated with dry hydrogen chloride. After filtration of the diphenylamine hydrochloride and washing with ether, the filtrate and washings were evaporated to dryness, giving a brown oil. This residue, dissolved in low-boiling light petroleum, was passed through a short column of activated alumina. Elution with the same solvent and evaporation of the effluent gave a white, crystalline solid (0·6 g.), m. p. 105—112°. Two crystallisations from methanol afforded pure 1-methylphenanthrene, m. p. 120—121° (Found: C, 93·2; H, 6·5. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·3%). The hydrocarbon formed a picrate, m. p. 134—135°, and a styphnate, m. p. 149—150°. Haworth (*J.*, 1932, 1125) gives 1-methylphenanthrene, m. p. 118°, picrate m. p. 139°, styphnate m. p. 149—150°; Bachmann and Wilds (*J. Amer. Chem. Soc.*, 1938, **60**, 624) give 1-methylphenanthrene m. p. 120—121°, picrate m. p. 136—136·5°.

Addition of 1-*Vinyl*cyclo*hex*-1-*ene to Toluquinone.*—A mixture of 1-vinyl*cyclo*hex-1-ene (5 g.) and toluquinone (5 g.) in benzene (75 c.c.) was heated under reflux for 4 hours. On removal of the solvent under reduced pressure, the residual oil was dissolved in a mixture of methanol (100 c.c.) and water (30 c.c.) and kept at 0° overnight. The resultant crop of fine, pale yellow needles, m. p. 99—101°, was collected (crop A, 2·12 g.). The filtrate, together with the methanol washings (10 c.c.) of crop A, was diluted with water (10 c.c.) and again cooled overnight, giving a further quantity of solid (crop B, 1·62 g.), m. p. below 75°. Two further dilutions with water (10 c.c. and 5 c.c.) gave more crystalline solid of low m. p. (crop C, 0·51 g.; crop D, 0·46 g.). The final mother-liquors gave only oily material on dilution with water.

Crop A, on recrystallisation from aqueous methanol, gave pale yellow needles of $\Delta^{2:9(14)}$-*decahydro*-1 : 4-*diketo*-2(or 3)-*methylphenanthrene* (XIX), m. p. 100—102° (Found: C, 77·8; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%). Crops B, C, and D were combined, and, after several crystallisations from aqueous methanol, gave pale yellow prisms, m. p. 94—95°, depressed to 68—90° on admixture with the needles of m. p. 100—102° (above). This material, m. p. 94—95°, was doubtless the isomeric *decahydrodiketomethylphenanthrene* (XIX) (Found: C, 77·8; H, 7·9. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%).

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118. *The Constitution of Yohimbine and Related Alkaloids. Part VI.* The Synthesis of* 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro-2-ketoindolo*-(2 : 3-a)*pyridocoline and* 1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline.*†

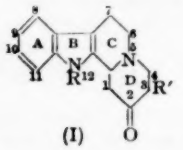
By L. H. Groves and G. A. Swan.

The compounds (I; R = R′ = H) and (II), named in the title, have been synthesised as a step towards further synthetic work in the field of the indole alkaloids. Both of these compounds have been converted into 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydroindolo(2 : 3-*a*)pyridocoline.

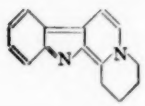
After the synthesis of yohimbone (Part IV, *J.*, 1950, 1534), synthesis of yohimbine requires also the introduction of the carbomethoxy-group. From Birch's work (*J.*, 1950, 1551) on the methyaltion of 2 : 5-dihydroanisole it appeared that this might be done *via* the potassium salt of 3″-methoxy-3 : 4 : 6 : 9*b* : 1″ : 4″-hexahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline. Accordingly, attempts were made first to introduce the carbethoxy-group into 2 : 5-dihydroanisole by Birch's method except that the methyl iodide was replaced by ethyl carbonate or chloroformate; but these attempts were unsuccessful.

At this stage we were also interested in obtaining *m*-methoxyphenylalanine in quantity, for the preparation of 6-methoxy*iso*quinoline-3-carboyxlic acid, since the introduction of a (potential) carbomethoxy-group into position 5 of this compound (as opposed to its 1 : 2 : 3 : 4-tetrahydro-derivative) seemed feasible. We also investigated two further methods for the preparation of *m*-methoxyphenylalanine; and these are described in the Experimental section, although the yields obtained are no better than those recorded in Part IV.

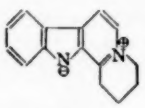
Even before these failures, attention was also turned to other synthetic routes and it seemed likely that ketones of type (I) might be useful starting materials for the synthesis, not only of yohimbine, but also of certain other alkaloids and degradation products thereof:



(I)



(II)



(IIa)

recent work on corynantheine (Karrer, Schwyzer, and Flam, *Helv. Chim. Acta*, 1951, **34**, 993; Janot, Goutarel, and Prelog, *ibid.*, p. 1207), serpentine (Schlittler and Schwarz, *ibid.*, 1950, **33**, 1463), and the alstonia alkaloids (Karrer and Enslin, *ibid.*, p. 100; Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506) has emphasised the importance of this ring system. We now describe preliminary experiments which have led to the syntheses of (I; R = R′ = H) and (I; R = Me, R′ = H) by methods which might allow extension to products in which R′ is some other group. In the case of serpentine and the alstonia alkaloids, ring c has the less reduced form as in (II), and we describe also a synthesis of this compound.

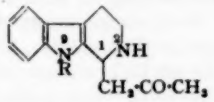
Tryptamine hydrochloride condensed with αγ-diketovaleric acid in water at 45°, or with formylacetone dimethyl acetal at room temperature, to give 1-acetonyl-1 : 2 : 3 : 4-tetrahydro-β-carboline ‡ (III; R = H). 1-Methyltryptamine similarly yielded (III; R = Me). Attempts to cyclise these compounds to (I; R = R′ = H) and (I; R = Me, R′ = H), respectively, by treatment with formaldehyde failed, so (IV; X = OMe and Cl) were synthesised. The latter, 1-(4-chloro-2-ketobutyl)-1 : 2 : 3 : 4-tetrahydro-β-carboline,

* Part V, *J.*, 1950, 1539.

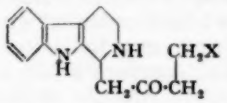
† Ring Index numbering and names (no. 2420) are used, except that pyridocoline is used in place of quinolizine.

‡ Ring Index numbering for carboline will be used in this and succeeding papers of this series.

was obtained as the hydrochloride in mediocre yield by condensing tryptamine with 2-chloroethyl 2-chlorovinyl ketone, and, on subsequent treatment with alkali, yielded a yellow resin. The action of sodium methoxide (2 mols.) in methanol on this ketone afforded 2 : 2-dimethoxyethyl 2-methoxyethyl ketone, which condensed smoothly with tryptamine hydrochloride, to give 1 : 2 : 3 : 4-tetrahydro-1-(2-keto-4-methoxybutyl)-β-carboline (IV; X = OMe). Attempts to cyclise this to (I; R = R′ = H) gave only resins.

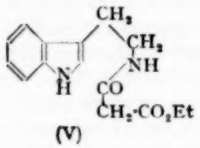


(III)



(IV)

Next, the synthesis of 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetic acid (VI; R = R′ = H) was investigated. Tryptamine and carbethoxyacetyl chloride gave the amide (V) as a gum which was cyclised by phosphoric oxide in xylene to the ethyl ester (VI; R = H, R′ = Et) of the required acid in low yield. Condensation of tryptamine with ethyl ethoxymethylenemalonate yielded a crystalline product, the analysis of which agreed with that for the expected derivative (VII). Attempts to convert (VII) into (VI; R = R′ = H) were unsuccessful, the compound being readily hydrolysed to tryptamine by alkali or acid. A condensation product of similar properties was also obtained from 2-phenylethylamine and ethyl ethoxymethylenemalonate. Finally, 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetic acid was obtained in satisfactory yield by condensing tryptamine hydrochloride with oxaloacetic acid in water at 40°, and was converted into the ethyl ester (VI; R = H, R′ = Et) by ethanolic hydrogen chloride. Similar condensation of tryptamine hydrochloride and carbethoxypyruvic acid afforded a mixture of the acid (VI; R = R′ = H) and its ester in combined yield greater than that of the acid obtained above, so this is the preferred method of preparation.



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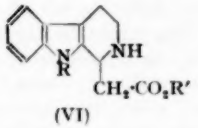

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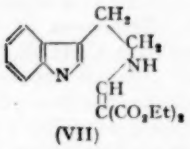


(VII)

Condensation of the ester (VI; R = H, R′ = Et) with vinyl cyanide and with ethyl acrylate afforded respectively ethyl 2-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate and diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-β-propionate (VIII; R = H, R′ = CN or CO_2Et, respectively), the latter in higher yield. Attempts to effect a similar condensation with ethyl β-chloro- or β-bromo-propionate were futile. The ester (VI; R = H, R′ = Et) condensed with ethyl ethoxymethylenemalonate, but hydrogenation of the product in ethanol in presence of Adams's catalyst caused fission to the original monoester. When the ester (VIII; R = H, R′ = CO_2Et) was subjected to a Dieckmann reaction and the product was hydrolysed with dilute hydrochloric acid, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydro-2-ketoindolo(2 : 3-*a*)pyridocoline (I; R = R′ = H) was obtained.

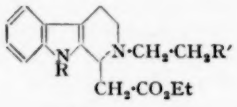
It seemed that, in an application of a reaction first used by du Feu, McQuillin, and Robinson (*J.*, 1937, 53), the action of 4-diethylaminobutan-2-one methiodide on the sodium salt of (I; R = R′ = H) might yield " base D " and/or " base E " described in Part IV. If this could be effected, a further extension might afford a synthesis of yohimbine. Experiments to bring about the Mannich base condensation were, however, unsuccessful, possibly on account of the presence of the acidic hydrogen atom of the indole nucleus. Attempts to acetylate (I; R = R′ = H) at this position were not encouraging, so the synthesis of (I; R = Me, R′ = H) was investigated.

1-Methyltryptamine and carbethoxypyruvic acid yielded ethyl 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline-1-acetate (VI; R = Me, R′ = Et). This with vinyl cyanide gave only a low yield of ethyl 2-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline

(VIII; R = Me, R′ = CN), and a similar reaction with ethyl acrylate produced a product which failed to crystallise either as the base or as the hydrochloride. However, Dieckmann cyclisation and hydrolysis of this crude product afforded the desired ketone (I; R = Me, R′ = H) in low yields which have not allowed further work.

With a view to the synthesis of de-ethylcoryline or coryline (alstyrine), the preparation of (I; R = H, R′ = Et) was also attempted. The reaction between (VI; R = H, R′ = Et) and ethyl α-ethylacrylate did not proceed smoothly as with ethyl acrylate; so condensation with ethyl α-formylbutyrate, followed by hydrogenation of the product, as used in an analogous case by Battersby and Openshaw (*Experientia*, 1950, **6**, 378), was investigated. Dr. Openshaw kindly communicated to us, before their publication, details of the experimental conditions employed in the latter work; but, even using these conditions, we were unable to isolate the required products from (VI; R = H or Me, R′ = Et).

Concurrently with the above work, synthesis of (II) was carried out. Tryptamine hydrochloride condensed with δ-hydroxyvaleraldehyde in water at 45°, to give 1-4′-hydroxybutyl-1 : 2 : 3 : 4-tetrahydro-β-carboline (IX) in good yield. This was smoothly dehydrogenated in presence of palladium black at 160° to give (X; X = OH), which reacted with hydrobromic acid to form the hydrobromide of 1-4′-bromobutyl-β-carboline (X; X = Br).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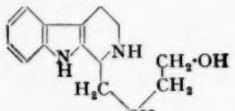
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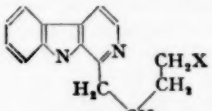
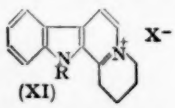

(X)

The base (X; X = Br) liberated from the above hydrobromide by the action of 1 equivalent of sodium carbonate very rapidly underwent internal quaternisation to give the colourless 1 : 2 : 3 : 4-tetrahydro-12*H*-indolo(2 : 3-*a*)pyridocolinium bromide (XI; R = H, X = Br). Treatment of the latter with excess of sodium hydroxide yielded a yellow crystalline base, $C_{15}H_{14}N_2,H_2O$. This might be the quaternary hydroxide (XI; R = H, X = OH), a *pseudo*-base, *e.g.*, (XII), or a hydrate of the anhydro-base (II). Attempts to dehydrate the base over phosphoric oxide *in vacuo* at 70° gave a product which differed in melting point, solubility properties, absorption spectrum, and analytical results, the last suggesting that oxidation had taken place; so subsequent work was carried out on the product dried *in vacuo* at room temperatue. As seen from the figure, the ultra-violet absorption spectra of the bromide and the base in ethanol are not significantly different, except that the extinction coefficients are higher for the former. On the addition of sodium hydroxide, however, the three absorption maxima are all displaced bathochromically. These results are, on the whole, in good agreement with those recorded by Schwarz and Schlittler in the case of *N*-methylnorharman, serpentinine, serpentine, and *N*-methylyobyrine (*Helv. Chim. Acta*, 1951, **34**, 629). The yellow base is readily soluble in methanol and is not precipitated from the resulting solution by the addition of water; if, however, sodium hydroxide solution is added to the diluted solution, precipitation occurs. It may,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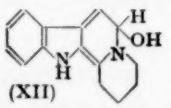
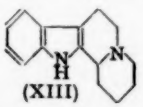

(XII)

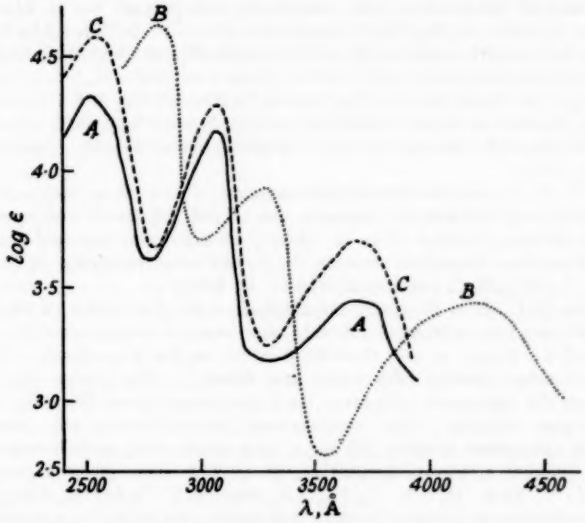

(XIII)

therefore, be concluded that in alcoholic solution the base exists largely as the quaternary hydroxide (XI; R = H, X = OH), but in presence of sodium hydroxide is transformed into the anhydro-base, which will exist as a resonance hybrid involving structures (II) and (II*a*). Treatment of the base with methyl iodide afforded a product formulated as the iodide (XI; R = Me, X = I). The ultra-violet absorption spectrum of this iodide is not appreciably changed in presence of sodium hydroxide, and is essentially the same as that of (XI; R = H, X = Br). These observations exclude the *pseudo*-base structure (XII) for the yellow base; for if this were correct, the absorption maxima of (XI; R = Me, X = I)

should be displaced bathochromically in presence of alkali, as in the case of the methyl-free compound.

Hydrogenation of (II) in ethanol in presence of Adams's catalyst yielded a colourless base, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydroindolo(2 : 3-*a*)pyridocoline (XIII), recognised as a derivative of 1 : 2 : 3 : 4-tetrahydro-β-carboline by its ultra-violet absorption spectrum which is similar to that of yohimbine, and by the characteristic colour reaction with concentrated sulphuric acid in presence of an oxidising agent (Part I, *J.*, 1946, 617). This colour reaction was given generally by the various compounds represented in this paper as derivatives of 1 : 2 : 3 : 4-tetrahydro-β-carboline. Those substances, however, in which the indole-nitrogen atom is methylated, gave an extremely transient reddish-purple colour (instead of blue), changing to olive-green in a few seconds. The test failed in the case of 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline itself.

The hydroxyl group of (IX) was replaced by bromine on treatment of the substance with hydrobromic acid, the yield being very low. When (IX) was treated with hydrogen



A, 1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline in ethanol.*
B, The same in 0·015N-*ethanolic sodium hydroxide.*
C, 1: 2 : 3 : 4-*Tetrahydro*-12H-*indolo*(2 : 3-a)*pyridocolinium bromide in ethanol.*

chloride and triphenyl phosphite (cf. Landauer and Rydon, *Chem. and Ind.*, 1951, 313) and the product was basified with sodium hydroxide, (XIII) was obtained in low yield. The ketone (I; R = R′ = H) has also been converted into this substance by the Wolff–Kishner reduction, although the yield obtained was low, the main product being another base, the structure of which is uncertain. However, the identity of the product obtained in this way and by hydrogenation of (II) was established. The formation of the other product in the Wolff–Kishner reduction is not unexpected in view of the known instability of β-amino-ketones under alkaline conditions. It was thought that the action of Raney nickel on a thioketal of (I; R = R′ = H) might afford a better method of conversion. As a model, the reaction was tried on yohimbone, but the action of Raney nickel in boiling ethanol left its thioketal largely unchanged.

The reduction of 3-carbamylindole with lithium aluminium hydride was investigated as a possible preparative method for tryptamine, but the yield obtained was too low to be of value. Attempts to prepare γ-aminobutaldehyde phenylhydrazone (which can be cyclised to tryptamine) by the condensation of nitrosobenzene with 1 : 4-diaminobutane failed, although acetaldehyde phenylhydrazone was obtained from nitrosobenzene and ethylamine.

Experimental

M. p.s are uncorrected

1-*Acetonyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline* (III; R = H).—(*a*) A solution of tryptamine hydrochloride (0·5 g.) and αγ-diketovaleric acid (0·75 g.) (Lehninger and Witzemann, *J. Amer. Chem. Soc.*, 1942, **64**, 874) in water (7·5 ml.) was heated at 45° for 2 days, cooled, basified (sodium hydroxide solution), and extracted with ether. The extract was dried (K_2CO_3), acidified with methanolic hydrogen chloride, and cooled in ice. The *hydrochloride* (0·59 g.) was collected, washed with ether, and recrystallised from ethanol as colourless, felted needles (0·45 g.), still unmelted at 320° (Found: C, 63·3; H, 6·75. $C_{14}H_{17}ON_2Cl$ requires C, 63·5; H, 6·45%). A solution of this in water was basified (sodium hydroxide solution) and extracted with ether; the extract was dried (K_2CO_3) and the solvent was removed, leaving the *base* as a gum which eventually crystallised. This separated from light petroleum (b. p. 60—80°) as pale yellow crystals, m. p. 102—103° (Found: C, 73·65; H, 7·25. $C_{14}H_{16}ON_2$ requires C, 73·75; H, 7·0%). The *picrate* separated from ethanol as light orange prisms, m. p. 164—165° (decomp.) (Found: C, 52·65; H, 4·0. $C_{14}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 52·5; H, 4·15%). The *semicarbazone hydrochloride* separated from ethanol as cream-coloured prisms, m. p. 241—242° (decomp.) (Found: C, 55·9; H, 6·2. $C_{15}H_{20}ON_5Cl$ requires C, 56·0; H, 6·2%). The *benzoyl* derivative, prepared by the Schotten–Baumann method in presence of ether, separated from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 133° (Found: C, 75·6; H, 5·8. $C_{21}H_{20}O_2N_2$ requires C, 75·9; H, 6·0%). (*b*) A solution of tryptamine hydrochloride (0·3 g.) in water (5 ml.) was treated with formylacetone dimethyl acetal (0·5 g.) (Price and Pappalardo, *J. Amer. Chem. Soc.*, 1950, **72**, 2613) and the mixture kept at room temperature for 2 days. Isolation as in (*a*) gave the hydrochloride (0·2 g.).

1-*Acetonyl*-1 : 2 : 3 : 4-*tetrahydro*-9-*methyl*-β-*carboline* (III; R = Me).—A solution of 1-methyltryptamine (0·2 g.) (Späth and Lederer, *Ber.*, 1930, **63**, 2102) and αγ-diketovaleric acid (0·45 g.) in water (3 ml.), treated as in (*a*) above, afforded the *hydrochloride* (0·13 g.) which separated from ethanol as colourless crystals, m. p. 240° after sintering at 168—170° (Found: C, 64·5; H, 6·9. $C_{15}H_{19}ON_2Cl$ requires C, 64·65; H, 6·8%).

Reaction between (III; R = H) *and Formaldehyde.*—(*a*) A solution of the hydrochloride of (III; R = H) (100 mg.) in methanol (20 ml.) was treated with paraformaldehyde, and the mixture was heated for 2 days at 45°, then for 8 hours on the water-bath. The methanol was removed and the residue treated with water and filtered. The filtrate was basified (sodium hydroxide solution) and extracted with ether, and the extract dried (Na_2SO_4) and acidified with methanolic hydrogen chloride. The precipitated hydrochloride was recrystallised from methanol, forming colourless needles (20 mg.), and under Schotten–Baumann conditions in presence of ether yielded a *benzoyl* derivative, m. p. 171—172° [from light petroleum (b. p. 80—100°)] (Found: C, 73·2; H, 6·2. $C_{22}H_{22}O_3N_2$ requires C, 72·85; H, 6·1%).

(*b*) A 0·8% formaldehyde solution (4 ml.; 1·5 mols.) was added to a solution of the hydrochloride of (III; R = H) (0·2 g.) in a phosphate buffer solution of pH 6 (5 ml.). After a few minutes the solution became turbid and deposited a yellow, flocculent solid, which was collected at the end of 1 hour. This solid was shaken with a mixture of benzene and 10% sodium hydroxide solution until all was in solution, the benzene layer was dried (Na_2SO_4), and the solvent was removed, leaving a yellow base, m. p. 213—215° (decomp.), which could not be purified.

(*c*) Treatment of (III; R = H) with methylal and concentrated hydrochloric acid yielded only black, polymeric products.

2-Chloroethyl 2-Chlorovinyl Ketone.—By the general procedure of Catch, Elliot, Hey, and Jones (*J.*, 1948, 278), without the use of a solvent, β-chloropropionyl chloride (13 g.) and aluminium chloride (15 g.) absorbed acetylene (1·3 g.) during 6 hours and afforded the ketone (9·2 g.), b. p. 88—94°/16 mm. (Found: C, 39·3; H, 4·3. Calc. for $C_5H_6OCl_2$: C, 39·25; H, 3·95%) [cf. D.R.-P. 642 147 (*Chem. Abs.*, 1937, **31**, 3501) and Yakubovich and Merkulova, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 55 (*Chem. Abs.*, 1947, **41**, 91)].

2 : 2-Dimethoxyethyl 2-Methoxyethyl Ketone.—A solution of sodium (0·62 g.) in methanol (10 ml.) was added dropwise to a stirred, ice-cold solution of the foregoing ketone (2 g.) in methanol (10 ml.). The mixture was set aside for 2 hours at room temperature and filtered from sodium chloride. The filtrate was evaporated at 30—35° under reduced pressure, the residue dissolved in chloroform, and the solution washed with dilute sodium hydrogen carbonate solution and dried (Na_2SO_4). The chloroform was removed at 30° under reduced pressure and the residue distilled giving *2 : 2-dimethoxyethyl 2-methoxyethyl ketone* as a colourless oil (0·85 g.), b. p.

103—104°/14 mm. (Found: C, 54·3; H, 9·2; MeO, 51·6. $C_6H_{10}O_4$ requires C, 54·55; H, 9·1; MeO, 51·8%).

When the amount of sodium used was halved, the *product* was a colourless oil (0·6 g.), b. p. 70—74°/13 mm. (Found: C, 48·3; H, 6·3; MeO, 21·2. C_6H_9OCl requires C, 48·5; H, 6·1; MeO, 20·9%). This failed to condense with tryptamine hydrochloride. A solution containing this product (0·6 g.) and dimethylamine (1 g.) in methanol (15 ml.) was kept at room temperature overnight. The methanol was removed, the residue shaken with ether and sodium hydroxide solution, the ethereal layer separated, and the aqueous layer extracted with ether. The residue from the dried (Na_2SO_4) extract distilled as a pale yellow oil (0·42 g.), b. p. 123—127°/2 mm. (Found: C, 61·4; H, 9·6. $C_8H_{15}O_2N$ requires C, 61·15; H, 9·55%). When a solution containing this *substance* (0·1 g.) and methyl iodide (0·2 g.) in dry benzene (1 ml.) was kept overnight at 8°, a *salt* separated which after recrystallisation from methanol formed colourless needles, m. p. 183—184° (decomp.) (Found: C, 38·5; H, 6·25. $C_{10}H_{20}O_2NI$ requires C, 38·35; H, 6·4%).

1-(4-*Chloro*-2-*ketobutyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline* (IV; X = Cl).—A mixture of tryptamine (0·24 g.), benzene (5 ml.), and 10% sodium carbonate solution (5 ml.) was cooled in ice and stirred vigorously while a solution of 2-chloroethyl-2-chlorovinyl ketone (0·24 g.) in benzene (5 ml.) was added during 15 minutes, and then stirred for 30 minutes longer. The benzene layer was separated and the aqueous layer was extracted with chloroform. The combined organic extracts were dried (Na_2SO_4) and evaporated, leaving a gummy residue which was dissolved in acetone and acidified with methanolic hydrogen chloride. A tar was precipitated, followed, slowly, by 1-(4-*chloro*-2-*ketobutyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline hydrochloride* and this was separated from the tar by decantation and recrystallised from methanol–acetone (charcoal), giving colourless crystals (0·1 g.) m. p. > 300° (Found: C, 57·1; H, 5·95. $C_{15}H_{18}ON_2Cl_2$ requires C, 57·5; H, 5·75%).

1 : 2 : 3 : 4-*Tetrahydro*-1-(2-*keto*-4-*methoxybutyl*)-β-*carboline* (IV; X = OMe).—Tryptamine hydrochloride (0·85 g.) was condensed with 2 : 2-dimethoxyethyl-2-methoxyethyl ketone (1·1 g.) in water (15 ml.), as in the preparation of (III; R = H) by method *b*, and yielded a crude *hydrochloride* (0·75 g.) which, after recrystallisation from methanol–acetone, afforded colourless needles, m. p. >300° (Found: C, 62·9; H, 7·05; OMe, 9·9. $C_{16}H_{21}O_2N_2Cl$ requires C, 63·05; H, 6·9; OMe, 10·0%). The base failed to crystallise, but the *benzoyl* derivative separated from light petroleum (b. p. 80—100°) as short, colourless needles, m. p. 152—153° (Found: C, 73·1; H, 6·7. $C_{23}H_{24}O_3N_2$ requires C, 73·4; H, 6·4%).

Condensation of Tryptamine with Ethyl αγ-*Diketovalerate*.—When a solution of tryptamine (50 mg.) in benzene (3 ml.) was treated with ethyl αγ-diketovalerate (50 mg.) (*Org. Synth.*, **6**, 40), a semi-solid mass separated almost immediately. The mixture was diluted with light petroleum (b. p. 40—60°) and cooled and the *substance* (0·1 g.) produced recrystallised from benzene as colourless crystals, m. p. 106—107° (decomp.) (Found: C, 63·9; H, 6·7. $C_{17}H_{22}O_4N_2$ requires C, 64·2; H, 6·9%).

A similar reaction with 2-phenylethylamine (0·5 g.) and ethyl αγ-diketovalerate (0·66 g.) yielded a *substance* as colourless, felted needles (1 g.), m. p. 124° (decomp.) (Found: C, 64·7; H, 7·85. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·55%). Attempted dehydration of the material with magnesium sulphate in boiling benzene yielded a gum; and it was readily hydrolysed by dilute hydrochloric acid (water-bath) to 2-phenylethylamine.

3-2′-(2″ : 2″-*Dicarbethoxyvinylamino*)*ethylindole* (VII).—A mixture of tryptamine (1 g.) and ethyl ethoxymethylenemalonate (1·36 g.) was heated for 1 hour on the water-bath and then cooled in ice with stirring, whereupon it solidified. The *indole* derivative produced was stirred with light petroleum and recrystallised first from dilute ethanol, then from light petroleum (b. p. 60—80°), affording colourless prisms (1·4 g.), m. p. 93·5—94·5° (Found: C, 65·45; H, 7·1. $C_{16}H_{22}O_4N_2$ requires C, 65·45; H, 6·7%).

Ethyl 2′-*Phenylethylaminomethylenemalonate*.—The reaction between 2-phenylethylamine (0·48 g.) and ethyl ethoxymethylenemalonate (1 g.) (3 hours; water-bath) afforded a colourless, viscous *ester* (0·8 g.), b. p. 206—208°/2 mm. (Found: C, 65·8; H, 7·1. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2%). The same product (0·7 g.) was obtained by shaking the reactants suspended in water (10 ml.) for 24 hours at room temperature.

1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetic Acid* (VI; R = R′ = H).—(*a*) A solution of carbethoxyacetyl chloride (0·24 g.) in benzene (4 ml.) was added during 20 minutes to a vigorously stirred mixture of tryptamine (0·25 g.), benzene (9 ml.), and 0·5N-sodium hydroxide (3 ml.). After being stirred for a further 20 minutes, the mixture was basified (sodium hydroxide solution), the benzene layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed successively with 2N-sodium hydroxide, 2N-hydrochloric

acid, and 2N-sodium hydroxide, and dried (K_2CO_3). Evaporation of the organic solvents yielded a gum (0·22 g.) which was dissolved in xylene (10 ml.). The boiling solution, in an atmosphere of nitrogen, was treated with phosphoric oxide (2·5 g.) during 45 minutes. The mixture was heated under reflux for 1 hour longer, cooled, and treated with dilute hydrochloric acid (to give a clear solution), and the aqueous layer was extracted with ether, then basified (sodium hydroxide), and again extracted with ether. The last extract was dried (K_2CO_3) and acidified with ethanolic hydrogen chloride. The crude hydrochloride thus precipitated was hydrogenated immediately in ethanol in presence of palladium–charcoal, at ordinary temperature and pressure. The filtered solution on evaporation yielded the *ethyl* ester *hydrochloride*, which separated from ethanol as colourless needles (20 mg.), m. p. 240° (decomp.) (Found: C, 61·25; H, 6·5. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·05; H, 6·75%).

(*b*) A solution of tryptamine hydrochloride (0·75 g.) and oxaloacetic acid (0·75 g.) (Heidelberger and Hulbert, *J. Amer. Chem. Soc.*, 1950, **72**, 4704) in water (10 ml.) was heated at 45° for 1½ hours, then cooled, and the *acid* filtered off, washed with water, and boiled with methanol to remove impurities, whereupon colourless crystals (0·49 g.), m. p. 223—224° (decomp.), remained (Found: C, 62·7; H, 6·1. $C_{13}H_{14}O_2N_2,H_2O$ requires C, 62·9; H, 6·45%). A mixture of this acid (2 g.) and ethanol (40 ml.) was saturated at 0° with hydrogen chloride and then heated under reflux overnight. The solution was concentrated to a small volume, then cooled, and the ethyl ester hydrochloride (2 g.) was collected, washed with acetone, and recrystallised from ethanol as colourless needles, m. p. 240° (decomp.) (Found: C, 61·1; H, 6·45. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·05; H, 6·75%). The *ethyl* ester *picrate* separated from ethanol as orange needles, m. p. 204—205° (decomp.) (Found: C, 51·55; H, 4·4. $C_{15}H_{18}O_2N_2,C_6H_3O_7N_3$ requires C, 51·75; H, 4·3%). The *ethyl* ester *benzoyl* derivative formed colourless needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 180° (Found: C, 72·5; H, 6·1. $C_{22}H_{22}O_2N_2$ requires C, 72·9; H, 6·1%). The ethyl ester (VIII; R = H, R′ = Et) liberated by alkali from the hydrochloride formed a gum. The *methyl* ester *hydrochloride* separated from methanol–acetone as colourless needles, m. p. 225° (decomp.) (Found: C, 59·5; H, 5·7. $C_{14}H_{17}O_2N_2Cl$ requires C, 59·9; H, 6·05%). The *methyl* ester *picrate* separated from ethanol as orange needles, m. p. 197—197·5° (Found: C, 50·35; H, 4·2. $C_{14}H_{16}O_2N_2,C_6H_3O_7N_3$ requires C, 50·75; H, 4·0%).

(*c*) Carbethoxypyruvic acid was prepared by a modification of Wislicenus's method (*Annalen*, 1888, **246**, 306). A mixture of diethyl sodio-oxaloacetate (10 g.), water (75 ml.), and 1 equiv. of sodium hydroxide (48 ml.; 0·872N.) was shaken for 3 minutes, then acidified with 4N-sulphuric acid and extracted with ether (6 × 60 ml.). The solvent was removed (finally in a vacuum) from the dried (Na_2SO_4) extract, and the residue washed with a little ice-cold carbon tetrachloride, affording carbethoxypyruvic acid, m. p. 98—100° (Wislicenus and Endres, *Annalen*, 1902, **321**, 372, give m. p. 102—103°), the yield varying from 1·5 to 3·1 g.

A solution of tryptamine hydrochloride (0·8 g.) and the above acid (0·9 g.) in water was heated at 40° for 15 hours. The acid (VI; R = R′ = H) (0·43 g.) was collected and the filtrate basified (sodium hydroxide solution) and extracted with ether. The dried (Na_2SO_4) extract was acidified with methanolic hydrogen chloride, giving the ethyl ester hydrochloride (0·47 g.).

Ethyl 2-2′-Cyanoethyl-1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate (VIII; R = H, R′ = CN).—A mixture of the ester (VI; R = H, R′ = Et) (0·17 g.) and vinyl cyanide (0·8 g.) was heated under reflux overnight, the excess of vinyl cyanide removed, the residue dissolved in ether, and the solution acidified with methanolic hydrogen chloride. The precipitated gum was triturated with a little acetone, and the resulting *hydrochloride* was recrystallised from methanol–acetone, forming colourless plates, m. p. 179·5—180·5° (80 mg.) (Found: C, 62·35; H, 6·4. $C_{18}H_{22}O_2N_3Cl$ requires C, 62·2; H, 6·35%).

Diethyl 1 : 2 : 3 : 4-Tetrahydro-β-carboline-1-acetate-2-propionate (VIII; R = H, R′ = CO_2Et).—A mixture of the ester (VI; R = H, R′ = Et) (3 g.) and ethyl acrylate (20 ml.) was heated in a sealed tube at 130° for 15 hours. The excess of ethyl acrylate was removed by distillation under reduced pressure and the residue was dissolved in ether and acidified with methanolic hydrogen chloride. The precipitated gum solidified when stirred with acetone (7 ml.), giving the diester *hydrochloride* (3 g.) which was filtered off and washed with acetone–ether (2 : 1). This separated from methanol–ether as colourless crystals, m. p. 147—148° (decomp.) (Found: C, 60·55; H, 6·85. $C_{20}H_{27}O_4N_2Cl$ requires C, 60·85; H, 6·85%). Basification gave the *diester* which separated from light petroleum (b. p. 40—60°) as colourless crystals, m. p. 77·5—78·5° (Found: C, 67·1; H, 7·4. $C_{20}H_{26}O_4N_2$ requires C, 67·05; H, 7·3%).

Ethyl 2-(2 : 2-Dicarbethoxyvinyl)-1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate.—The ester (VI; R = H, R′ = Et) (0·5 g.) and ethyl ethoxymethylenemalonate (0·42 g.) were heated together on the water-bath for 2 hours. Trituration with light petroleum (b. p. 40—60°) then yielded a

light brown solid (0·55 g.; m. p. 111—118°), which was recrystallised first from benzene–light petroleum (b. p. 60—80°) and then from dilute ethanol, affording the *triester* as colourless crystals (0·45 g.), m. p. 134—134·5° (Found: C, 64·2; H, 6·9. $C_{23}H_{28}O_6N_2$ requires C, 64·5; H, 6·55%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro*-2-*ketoindolo*(2 : 3-a)*pyridocoline* (I; R = R′ = H).—A solution of the diester (VIII; R = H, R′ = CO_2Et) (1·2 g.) in benzene (10 ml.) was added with cooling to sodium ethoxide (from sodium, 0·11 g.), and the mixture was heated under reflux overnight. After the addition of 10% hydrochloric acid (30 ml.), the mixture was heated on the water-bath for 6 hours, and then evaporated to dryness in a vacuum. The residue was dissolved in water, and the resulting solution was basified (sodium hydroxide solution) and extracted with ether. The extract was dried (Na_2SO_4) and the ether was removed. The residue (0·55 g.) was recrystallised from a small volume of benzene, affording the *ketone* (0·4 g.) as colourless prisms, m. p. 180—180·5° (Found: C, 75·1; H, 7·1; N, 11·7. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 12·25%). The **2 : 4-*dinitrophenylhydrazone hydrochloride*** separated from acetic acid as orange crystals, m. p. 243° (decomp.) (Found: C, 52·25; H, 4·95. $C_{21}H_{21}O_4N_6Cl,1·5H_2O$ requires C, 52·15; H, 4·75%). The *semicarbazone* separated from ethanol as colourless crystals, m. p. 213—214° (decomp.) (Found: C, 61·25; H, 7·0. $C_{16}H_{19}ON_5,H_2O$ requires C, 60·95; H, 6·7%).

1 : 2 : 3 : 4-*Tetrahydro*-9-*methyl*-β-*carboline*-1-*acetic Acid* (VI; R = Me, R′ = H).—A solution of 1-methyltryptamine hydrochloride (1·85 g.) and carbethoxypyruvic acid (3 g.) in water (25 ml.) was kept at 40—45° for 2 days. The products were isolated as for (VI; R = R′ = H), the combined yield of the hydrochlorides of the acid and ester being about 1·3 g.; the former was esterified as before. The *ethyl* ester *hydrochloride* separated from methanol–acetone as colourless needles, m. p. 217° (Found: C, 62·05; H, 7·1. $C_{16}H_{21}O_2N_2Cl$ requires C, 62·2; H, 6·8%). The *acid hydrochloride*, crystallised from methanol, had m. p. 157—158° (Found: C, 59·85; H, 6·2. $C_{14}H_{17}O_2N_2Cl$ requires C, 59·9; H, 6·05%). The ethyl ester formed a gum.

Ethyl* 2-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-9-*methyl*-β-*carboline*-1-*acetate (VIII; R = Me, R′ = CN).—A mixture of the foregoing ester (0·1 g.) and vinyl cyanide (1 ml.), heated for 20 hours at 115° in a sealed tube, afforded the *hydrochloride* (10 mg.), m. p. 116—117°, of the cyano-compound (Found: C, 61·25; H, 7·2. $C_{20}H_{26}O_2N_2Cl$ requires C, 61·0; H, 7·1%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro*-2-*keto*-12-*methylindolo*(2 : 3-a)*pyridocoline* (I; R = Me, R′ = H).—The gum (0·3 g.) obtained by heating a mixture of (VI; R = Me, R′ = Et) (0·25 g.) and ethyl acrylate (2 ml.) for 18 hours at 130—135° in a sealed tube was heated for 12 hours on the water-bath with benzene (3 ml.) and sodium ethoxide (from sodium, 40 mg.). Hydrolysis and working up as for (I; R = R′ = H) yielded a gum (80 mg.) which slowly solidified in the cold. This product was washed with light petroleum (b. p. 40—60°) and passed through a column of alumina. Elution with benzene containing ethanol (2%) afforded a fraction which on evaporation yielded the *ketone* (10 mg.) as colourless crystals, m. p. 124—125°, after recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 75·5; H, 7·05. $C_{16}H_{18}ON_2$ requires C, 75·6; H, 7·1%).

***Reaction between Ethyl* 1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetate and Ethyl* α-*Formylbutyrate*.**—A solution of (VI; R = H, R′ = Et) (100 mg.) and ethyl α-formylbutyrate (70 mg.) in dry ether (1 ml.) was kept at room temperature for 48 hours. The solid *substance* (100 mg.) left after evaporation was recrystallised twice from benzene–light petroleum (b. p. 60—80°), then from a small volume of ether, and formed colourless crystals, m. p. 116—117° (Found: C, 62·7; H, 7·5. $C_{22}H_{29}O_5N_2,H_2O$ requires C, 62·85; H, 7·6%). This material did not absorb hydrogen in presence of Adams's catalyst and was hydrolysed to (VI; R = H, R′ = Et) by warming it for 2 minutes on the water-bath with N-hydrochloric acid. Attempts to dehydrate it gave no new crystalline product. The same product was obtained after condensation and hydrogenation under the conditions used by Battersby and Openshaw. The latter conditions were also applied in the case of (VI; R = Me, R′ = Et); but here the product obtained was a gum which failed to crystallise even after being chromatographed and, when this gum was subjected to the treatment used in the Dieckmann cyclisation, a small amount of a product which failed to form a 2 : 4-dinitrophenylhydrazone resulted.

1 : 2 : 3 : 4-*Tetrahydro*-9-*methyl*-β-*carboline* (cf. Späth and Lederer, *loc. cit.*).—A solution of 1-methyltryptamine (0·2 g.) in 4% formaldehyde solution (2·2 ml.) kept at 40—45° for 1 day yielded the *hydrochloride* (0·18 g.), m. p. 273° (from methanol), of the carboline (Found: C, 64·7; H, 7·0. $C_{12}H_{15}N_2Cl$ requires C, 64·7; H, 6·75%). The *picrate* separated from ethanol as deep yellow crystals, m. p. 242° (decomp.) (Found: C, 52·0; H, 4·3. $C_{12}H_{14}N_2,C_6H_3O_7N_3$ requires C, 52·05; H, 4·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-4′-*hydroxybutyl*-β-*carboline* (IX).—A solution of tryptamine hydrochloride (1 g.) and δ-hydroxyvaleraldehyde (1 g.) in water (20 ml.) was kept at 45° for 2 days, and the product isolated as for the preparation of (III; R = H). The *hydrochloride* (1 g.) was precipitated as a gum which solidified on trituration with acetone and then separated from methanol–acetone as colourless needles, m. p. 192—193° (Found: C, 63·95; H, 7·65. $C_{15}H_{21}ON_2Cl$ requires C, 64·15; H, 7·5%). The *carboline* base had m. p. 154° (from benzene) (Found: C, 73·5; H, 8·35. $C_{15}H_{20}ON_2$ requires C, 73·75; H, 8·2%). The *picrate* separated from ethanol as orange crystals, m. p. 198—199° (Found: C, 53·1; H, 5·15. $C_{15}H_{20}ON_2,C_6H_3O_7N_3$ requires C, 53·25; H, 4·9%). The *picrolonate* separated from ethanol as yellow needles, m. p. 238—239° (Found: C, 58·75; H, 5·85. $C_{15}H_{20}ON_2,C_{10}H_8O_5N_4$ requires C, 59·05; H, 5·5%). When the hydrochloride (0·5 g.) was warmed on the water-bath for a few minutes with acetic acid (15 ml.), and the solution then allowed to cool, **1-4′-*acetoxybutyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline* *hydrochloride*** (0·5 g.) separated; from methanol–acetone this formed colourless needles, m. p. 214° (Found: C, 63·05: H, 7·05. $C_{17}H_{23}O_2N_2Cl$ requires C, 63·25; H, 7·1%). The corresponding *picrolonate* separated from ethanol as yellow crystals, m. p. 197° (Found: C, 58·85; H, 5·8. $C_{17}H_{22}O_2N_2,C_{10}H_8O_5N_4$ requires C, 58·9; H, 5·5%).

1-4′-*Hydroxybutyl*-β-*carboline* (X; X = OH).—A mixture of (IX) (1·4 g.) and palladium black (0·5 g.) was heated at 160°/10 mm. until hydrogen evolution ceased and for 10 minutes thereafter. The residue was extracted with methanol, and the filtrate was evaporated, leaving the *base* (1·3 g.; m. p. 165—169°), which separated from dilute methanol as colourless, glistening plates, m. p. 173° (1 g.) (Found: C, 75·0; H, 7·15. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7%). The dehydrogenation of (IX) or of 1 : 2 : 3 : 4-tetrahydro-β-carboline itself was not satisfactorily brought about by lead tetra-acetate in acetic acid or by chloranil or Raney nickel in xylene.

1-4′-*Bromobutyl*-β-*carboline* (X; X = Br) ***Hydrobromide***.—A solution of the foregoing compound (0·35 g.) in concentrated hydrobromic acid (20 ml.) was heated under reflux for 30 minutes, then evaporated to dryness in a vacuum. The residue was dissolved in methanol, and the resulting solution diluted with acetone. A small amount of flocculent material was removed and the filtrate was concentrated and diluted with ether, to precipitate the *bromo*-compound *hydrobromide* (0·5 g.) which separated from methanol–ether as colourless needles, m. p. 168—169° (Found: C, 47·05; H, 4·4. $C_{15}H_{16}N_2Br_2$ requires C, 46·9; H, 4·2%).

1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline* (II).—An aqueous solution of the foregoing hydrobromide (100 mg.) was briefly shaken with chloroform and sodium carbonate (13·8 mg., 1 equiv.), and the chloroform layer was then rapidly separated and cooled to 0°, whereupon it deposited crystals within a few minutes. These crystals (47 mg.) were removed and the filtrate was concentrated, a further crop (10 mg.) being obtained. This, **1 : 2 : 3 : 4-*tetrahydro*-12H-*indolo*(2 : 3-a)*pyridocolinium bromide*** (XI; R = H, X = Br), separated from methanol–acetone as fine, colourless needles, m. p. 280° (decomp.) (Found: C, 59·5; H, 5·2. $C_{15}H_{15}N_2Br$ requires C, 59·4; H, 4·95%). Light absorption in ethanol: $\lambda_{max.}$ 2540, 3060, and 3660 Å (log ε = 4·57, 4·27, and 3·67), $\lambda_{min.}$ 2790 and 3300 Å (log ε = 3·65 and 3·22). When an aqueous solution of this salt was basified with sodium hydroxide solution, the *base* (II) separated as yellow, felted needles, m. p. 80—81° after drying for 4 hours over potassium hydroxide in a vacuum-desiccator (Found: C, 74·5; H, 6·7. $C_{15}H_{14}N_2,H_2O$ requires C, 75·0; H, 6·7%). Light absorption in ethanol: $\lambda_{max.}$ 2510, 3070, and 3660 Å (log ε = 4·31, 4·16, and 3·43), $\lambda_{min.}$ 2780 and 3290 Å (log ε = 3·6 and 3·17). Light absorption in 0·015N-ethanolic sodium hydroxide solution: $\lambda_{max.}$ 2830, 3280, and 4200 Å (log ε = 4·63, 3·92, and 3·41), $\lambda_{min.}$ 3000 and 3540 Å (log ε = 3·69 and 2·75). Treatment of this base with methyl iodide produced **1 : 2 : 3 : 4-*tetrahydro*-12-*methylindolo*(2 : 3-a)*pyridocolinium iodide*** (XI; R = Me, X = I) which separated from methanol as pale brown needles, m. p. 276—277° after sintering at 263° (Found: C, 52·8; H, 5·2. $C_{16}H_{17}N_2I$ requires C, 52·75; H, 4·7%). Light absorption in ethanol: $\lambda_{max.}$ 2610, 3080, and 3775 Å (log ε = 4·49, 4·27, and 3·68), $\lambda_{min.}$ 2860 and 3330 Å (log ε = 3·90 and 3·11). Light absorption in 0·015N-ethanolic sodium hydroxide solution: $\lambda_{max.}$ 2600, 3080, and 3775 Å (log ε = 4·51, 4·16, and 3·63), $\lambda_{min.}$ 2860 and 3330 Å (log ε = 3·90 and 3·11).

1-4′-*Bromobutyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*.—A solution of (IX) (40 mg.) in acetic acid (9 ml.) and concentrated hydrobromic acid (1 ml.) was heated under reflux for 1 hour, then evaporated to dryness in a vacuum. A solution of the residue in methanol was diluted with acetone, and the precipitate removed. The filtrate was concentrated and diluted with ether, giving the *hydrobromide* (5 mg.) as almost colourless crystals, m. p. 190—191° after sintering at 180° (Found: C, 45·65; H, 5·8. $C_{15}H_{20}N_2Br_2,0{\cdot}5H_2O$ requires C, 45·35; H, 5·3%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydroindolo*(2 : 3-a)*pyridocoline* (XIII).—(*a*) A solution of the yellow base (II) (50 mg.) in ethanol (5 ml.) was shaken in presence of Adams's catalyst (20 mg.)

in an atmosphere of hydrogen at room temperature and pressure for 3 days. The filtered solution was evaporated to dryness, and the residue was dissolved in ether and acidified with methanolic hydrogen chloride. The *hydrochloride* (45 mg.) which separated as colourless crystals, after recrystallisation from ethanol, had m. p. 311—312° (Found : C, 64·5; H, 7·2. $C_{15}H_{19}N_2Cl,H_2O$ requires C, 64·2; H, 7·5%). The *base* separated from light petroleum (b. p. 60—80°) as colourless crystals, m. p. 147—147·5° (Found : C, 79·5; H, 8·2. $C_{15}H_{18}N_2$ requires C, 79·65; H, 8·0%). Light absorption in ethanol : $\lambda_{max.}$ 2790 Å (log ε = 3·89), $\lambda_{min.}$ 2470 Å (log ε = 3·33).

(*b*) A mixture of the base (IX) (0·1 g.), triphenyl phosphite (0·5 g.), and benzene (2 ml.) was saturated with dry hydrogen chloride at 0° and shaken overnight at room temperature; it was then basified (sodium hydroxide solution) and extracted with chloroform. The solvent was removed from the dried (Na_2SO_4) extract, and the residue was dissolved in acetone and acidified with methanolic hydrogen chloride. Dilution with ether afforded the *hydrochloride* (20 mg.), m. p. 311—312° after recrystallisation from ethanol, not depressed by admixture with the product from (*a*).

(*c*) A mixture of the ketone (I; R = R′ = H) (0·12 g.) and 90—95% hydrazine hydrate (1 ml.) was heated for 1 hour on the water-bath, cooled, and extracted with chloroform. The residue left after evaporation of the dried (Na_2SO_4) extract was heated with a solution of sodium (80 mg.) in ethanol (1·5 ml.) in a sealed tube for 18 hours at 165—175°. The mixture was then acidified with 2N-hydrochloric acid and evaporated to dryness in a vacuum. A solution of the residue in water was basified (sodium hydroxide solution), and extracted with ether, the extract dried (Na_2SO_4), and the solvent removed. Fractional crystallisation of the residue from benzene afforded two bases A and B, the latter being the more soluble. *Base A* (50 mg.) formed colourless crystals, m. p. 244° (decomp.), which gave the colour test for a 1 : 2 : 3 : 4-tetrahydro-β-carboline derivative [Found : C, 72·1, 72·55, 72·2; H, 8·1, 7·6, 7·9%; *M* (Rast) 255] and gave a colourless hydrochloride, m. p. 278° (from ethanol). Base B (10 mg.) was identical with (XIII) obtained as in (*a*) and admixture caused no depression of the m. p.

Reaction between Yohimbone and Ethanethiol.—A mixture of (−)-yohimbone (50 mg.), acetic acid (1 ml.), ethanethiol (0·1 g.), and a trace of hydrochloric acid was kept at room temperature overnight, *yohimbone diethyl thioketal hydrochloride* (50 mg.) separating as lustrous prisms, m. p. 290—292° after sintering at 250° (Found : C, 63·0; H, 7·6. $C_{23}H_{32}N_2S_2Cl$ requires C, 63·2; H, 7·6%).

3-Carbamylmethylindole.—A solution of 3-carboxymethylindole (1 g.) (Snyder and Pilgrim, *J. Amer. Chem. Soc.*, 1948, **70**, 3770) in methanol (20 ml.) was treated with one of diazomethane (0·25 g.) in ether (25 ml.), kept for 1 hour at 0°, washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solvents were removed, the residue was dissolved in a small volume of ether and mixed with aqueous ammonia (*d* 0·88; 12 ml.), and the whole was saturated at 0° with ammonia, then shaken in a stoppered bottle for 2 days at room temperature. Saturation and shaking were repeated twice, and the amide (0·83 g.) (m. p. 145—147°) collected and recrystallised from ethanol–light petroleum (b. p. 40—60°); it had m. p. 152—153°. Snyder and Pilgrim (*loc. cit.*) give m. p. 153°.

Tryptamine.—A solution of the above amide (0·5 g.) in dry tetrahydrofuran (6 ml.) was added dropwise in an atmosphere of nitrogen to one of lithium aluminium hydride (0·3 g.) in ether (30 ml.) and heated under reflux for 15 minutes. Water and dilute sulphuric acid were added and the organic layer was extracted with dilute sulphuric acid. The combined acid extracts were washed with chloroform, then basified (40% sodium hydroxide solution), and extracted again with chloroform. The latter extract was dried (K_2CO_3), the solvent removed, and the residue was dissolved in acetone, acidified with methanolic hydrogen chloride, and cooled in ice. The tryptamine hydrochloride, after being washed with acetone and recrystallised from methanol–acetone, had m. p. 248—249° (0·12 g.).

The bulk of the tryptamine used was prepared by the method of Schöpf and Steuer (*Annalen*, 1947, **558**, 124), the necessary β-cyanopropaldehyde diethyl acetal being made by Wohl's method (*Ber.*, 1906, **39**, 1951), although, in order to obtain the highest yield, it was found necessary to employ 0·5M-amounts of potassium iodide. Reduction to δ-aminobutaldehyde diethyl acetal by Wohl's method (*Ber.*, 1901, **34**, 1914) was effected in 70% yield.

Reaction between Nitrosobenzene and Ethylamine.—A solution of nitrosobenzene (2 g.) and ethylamine (1·4 g.) in benzene (10 ml.) was kept at room temperature for 4 days, then fractionated, yielding a yellow oil (0·7 g.), b. p. 70—73°/20 mm. (Bamberger and Pemsel give the b. p. of benzeneazoethane as 60—62°/12 mm.; *Ber.*, 1903, **36**, 53), and a brown oil (0·9 g.), b. p. 160°/2 mm. (Found : C, 75·2; H, 6·0%). The former fraction was heated for 3 minutes on the water-bath with a solution of sodium (0·18 g.) in ethanol (8 ml.), and the mixture then

poured into ice-water (25 ml.). The precipitated solid on recrystallisation from light petroleum (b. p. 60—80°) afforded light brown crystals (0·2 g.), m. p. 100—102°, not depressed on admixture with an authentic specimen of acetaldehyde phenylhydrazone, m. p. 102°.

m-*Methoxybenzyl Chloride*.—*m*-Methoxybenzyl alcohol was prepared from the aldehyde, by the general method of Carothers and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1675). Thionyl chloride (5·3 g.) was added dropwise to a mixture of the alcohol (5·1 g.) and dry pyridine (3·2 g.) in benzene (5 ml.) which was then kept overnight at room temperature, treated with water, and extracted with ether. The extract was washed thrice with sodium carbonate solution, dried (Na_2SO_4), and distilled, yielding the chloride (4·7 g.), b. p. 98—102°/4 mm.

*Ethyl α-Formamido-α-*m*-methoxybenzylmalonate*.—To a solution of sodium (0·28 g.) in absolute ethanol (20 ml.), ethyl formamidomalonate (2·47 g.) (Galat, *J. Amer. Chem. Soc.*, 1947, **69**, 965) and then a solution of *m*-methoxybenzyl chloride (1·85 g.) in ethanol (10 ml.) were added. The mixture was kept for 18 hours at room temperature, heated under reflux for 8 hours, and filtered. The bulk of the ethanol was removed in a vacuum and the residue was treated with water and extracted with chloroform. The extract was washed with water, then dried ($CaCl_2$), and the solvent was removed, leaving a gum, which crystallised on trituration with light petroleum (b. p. 40—60°). *Ethyl α-formamido-α-*m*-methoxybenzylmalonate* separated from dilute ethanol as colourless needles, m. p. 96—97° (1·8 g.) (Found: C, 59·4; H, 6·65. $C_{16}H_{21}O_6N$ requires C, 59·4; H, 6·5%).

This ester (0·8 g.) was heated under reflux for 45 minutes with a solution of potassium hydroxide (0·8 g.) in ethanol (8 ml.), then diluted with water (35 ml.), extracted with ether, cooled in ice, acidified (dilute hydrochloric acid), and again extracted with ether. The solvent was removed from the dried (Na_2SO_4) extract, and the residual gum solidified on cooling, yielding the colourless *acid* (0·42 g.), m. p. 128° (decomp.) (Found: C, 53·75; H, 4·6. $C_{12}H_{13}O_6N$ requires C, 53·9; H, 4·85%).

N-*Formyl*-β-m-*methoxyphenylalanine*.—The dibasic acid was decarboxylated at 100°/18 mm. (45 minutes); the product separated from water as colourless prisms, m. p. 156° (Found: C, 59·25; H, 6·2. Calc. for $C_{11}H_{13}O_4N$: C, 59·2; H, 5·8%). Chakravarti and Rao (*J.*, 1938, 172) give m. p. 156°.

β-m-*Methoxyphenylalanine*.—The *N*-formyl derivative (0·52 g.) was heated (water-bath) with 5% hydrochloric acid (7 ml.) for 4 hours in an atmosphere of nitrogen. The mixture was evaporated to dryness in a vacuum, and a solution of the residue in water (1·5 ml.) was adjusted to pH 5 with aqueous ammonia. After being kept overnight at 0°, the product (0·29 g.) was collected and formed colourless needles, m. p. 214—215° (decomp.).

m-*Methoxybenzyl Toluene*-p-*sulphonate*.—A mixture of *m*-methoxybenzyl alcohol (1 g.) and toluene-*p*-sulphonyl chloride (1·38 g.) in dry ether (8 ml.) was cooled in a freezing mixture and stirred vigorously while finely powdered potassium hydroxide (1·51 g.) was added in small portions, the temperature being kept below 4°. The mixture was stirred for 3 hours longer, shaken overnight at room temperature, treated with water, and extracted with chloroform. The extract was washed with water, then dried ($CaCl_2$), the solvent was removed, and the *ester* (1·4 g.) was recrystallised from benzene–light petroleum (b. p. 60—80°), giving colourless crystals, m. p. 83·5—84·5° (Found: C, 61·9; H, 5·7. $C_{15}H_{16}O_4S$ requires C, 61·65; H, 5·5%).

The yield of ethyl α-formamido-α-*m*-methoxybenzyl malonate obtained by condensation of ethyl formamidomalonate with this ester (1 g.) was only 0·38 g., *i.e.*, lower than with *m*-methoxybenzyl chloride.

m-*Methoxybenzylidenerhodanine*.—Anhydrous sodium acetate (5·45 g.) was added to a solution of *m*-methoxybenzaldehyde (5 g.) and rhodanine (4·9 g.) in acetic acid (14·5 ml.), and the mixture was boiled for 30 minutes with occasional shaking and poured into water (72 ml.). The *product* (8·45 g.; m. p. 225—227°) was collected, washed well with water, then with a little ethanol and ether. It separated from acetic acid as golden-yellow needles, m. p. 227° (Found: C, 52·45; H, 3·9. $C_{11}H_9O_2NS_2$ requires C, 52·7; H, 3·6%).

α-*Hydroxyimino*-β-m-*methoxyphenylpyruvic Acid*.—The above (2·9 g.) was heated on the water-bath for 5 minutes with 15% sodium hydroxide solution (15 ml.). The solution was cooled in a freezing mixture and acidified rapidly with 10% hydrochloric acid. The crude β-*m*-methoxyphenyl-α-thiopropionic acid (2·6 g.) was collected and washed with water.

A warm solution of hydroxylamine hydrochloride (5·16 g.) in water (5 ml.) was added to a solution of sodium (1·7 g.) in ethanol (50 ml.), and the precipitated sodium chloride removed by filtration. The above thio-acid was heated under reflux for 3 hours with this hydroxylamine solution, and the mixture then evaporated to dryness in a vacuum. The residue was dissolved in 5% sodium hydroxide solution (7 ml.), and the solution was centrifuged to remove sulphur,

cooled in ice, and acidified with 10% hydrochloric acid (12 ml.). The *hydroxyimino-acid* (1·85 g.), m. p. 130—135°, separated and after recrystallisation from water afforded colourless plates (1·4 g.), m. p. 138—140° (Found: C, 57·7; H, 5·2. $C_{10}H_{11}O_4N$ requires C, 57·45; H, 5·25%). Difficulty was experienced in attaining reproducible yields in this preparation, the initial 5 minutes' reaction time with sodium hydroxide being very critical.

β-m-*Methoxyphenylalanine*.—A solution of the hydroxyimino-acid (1·4 g.) in 10% sodium hydroxide solution (10 ml.) was warmed on the water-bath and, to it, 4% sodium amalgam (28 g.) was added during 15 minutes. After being cooled, the mercury was separated and the mixture was adjusted to pH 6 with acetic acid, boiled with charcoal, filtered, and concentrated to a small volume. The crude product which separated was purified *via* the copper salt, the yield then being 0·5 g., and the m. p. 215° (decomp.).

The light absorption data were determined by use of a Hilger Medium Quartz Spectrograph.

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119. *The Formation of Osazones. Part IV.* A Quantitative Study of the Reaction of Benzoin Phenylhydrazone with Phenylhydrazine.*

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A new mechanism for osazone formation has been proposed, based on the relative amounts of ammonia formed and phenylhydrazine consumed in the reaction of benzoin phenylhydrazone with phenylhydrazine. Aqueous acetic acid was used as solvent and the rate of acetylation of phenylhydrazine by this medium was also measured.

THE most commonly accepted mechanism for osazone formation may be illustrated as follows, with benzoin:

Mechanism (I)

$$HO{\cdot}CHPh{\cdot}CPh{:}O + Ph{\cdot}NH{\cdot}NH_2 \overset{(A)}{\rightleftharpoons} HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + H_2O$$

$$HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH{\cdot}NH_2 \xrightarrow{(B)} O{:}CPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH_2 + NH_3$$

$$O{:}CPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH{\cdot}NH_2 \xrightarrow{(C)} NHPh{\cdot}N{:}CPh{\cdot}CPh{:}N{\cdot}NHPh + H_2O$$

The most difficult stage of this mechanism to understand is stage (*B*) where phenylhydrazine acts in the unusual role of an oxidising agent. In order to explain this, Weygand (*Ber.*, 1940, **73**, 1284; *Chem. Ber.*, 1949, **82**, 438) assumed an Amadori rearrangement. Now, it has already been shown (Kenner and Knight, *Ber.*, 1936, **69**, 341; Bloink and Pausacker, *J.*, 1950, 1328) that osazone formation is favoured when substituted phenylhydrazines possess an electron-attracting group and is hindered when they possess an electron-repelling group, whereas the rate of hydrazone formation would be affected in the reverse order by these substituents (Conant and Bartlett, *J. Amer. Chem. Soc.*, 1932, **54**, 2881; Ardagh, Kellam, Rutherford, and Walstaff, *ibid.*, p. 721). In the Amadori rearrangement, each molecule of phenylhydrazine reacts with a carbonyl (or imine) group so that this explanation of stage (*B*) is incorrect. Recently, Braude and Forbes (*J.*, 1951, 1763) have overcome this objection by their ingenious and satisfactory explanation of stage (*B*).

Before mechanism (I) is accepted, another that has not been proposed previously should be considered.

* Part III, *J.*, 1951, 2212.

Mechanism (II)

$$HO{\cdot}CHPh{\cdot}CPh{:}O + Ph{\cdot}NH{\cdot}NH_2 \overset{(D)}{\rightleftharpoons} HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + H_2O$$

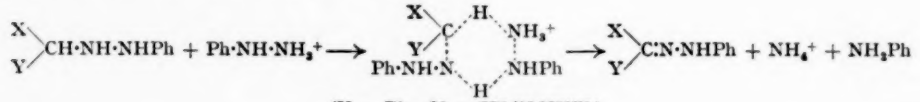
$$HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH{\cdot}NH_2 \overset{(E)}{\rightleftharpoons} NHPh{\cdot}NH{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + H_2O$$

$$NHPh{\cdot}NH{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH{\cdot}NH_2 \overset{(F)}{\longrightarrow} NHPh{\cdot}N{:}CPh{\cdot}CPh{:}N{\cdot}NHPh + Ph{\cdot}NH_2 + NH_3$$

The first stage (*D*) of this mechanism is the same as stage (*A*) of mechanism (I). The second stage (*E*) is supported by the work of Cowper and Stevens (*J.*, **1940**, **347**), who found that aniline condenses with benzoins with the formation of keto-amines; the mechanism of this stage could be represented as follows (cf. Cowper and Stevens, *loc. cit.*; Smith and Anderson, *J. Org. Chem.*, **1951**, **16**, 963) :

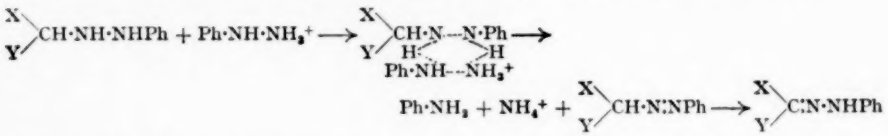
$$HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh \rightleftharpoons HO{\cdot}CPh{:}CPh{\cdot}NH{\cdot}NHPh \rightleftharpoons O{:}CPh{\cdot}CHPh{\cdot}NH{\cdot}NHPh \xrightleftharpoons{Ph{\cdot}NH{\cdot}NH_2} NHPh{\cdot}N{:}CPh{\cdot}CHPh{\cdot}NH{\cdot}NHPh$$

The third stage (*F*) could be represented in a manner analogous to that suggested by Braude and Forbes (*loc. cit.*) for stage (*B*) :



(X = Ph; Y = CPh:N·NHPh)

An alternative scheme, based on the fact that Franzen and Fürst (*Annalen*, **1917**, **412**, 29) found that 1-*o*-aminophenyl-2-benzylhydrazine is converted into benzaldehyde *o*-aminophenylhydrazone, benzylamine, and *o*-phenylenediamine, is as follows :



However, this does not explain the formation of osazones with 1-methyl-1-phenylhydrazine, as an intermediate azo-compound would not be possible.

By measuring the value of the ratio between phenylhydrazine consumed and ammonia formed during the reaction of benzoin phenylhydrazone with phenylhydrazine, it should be possible to distinguish between mechanisms (I) and (II). With mechanism (I) this value should be initially less than two, whereas with mechanism (II) it should be initially greater than two. Both should, of course, approach two at infinite time.

The investigation of this reaction was complicated by two factors : (*a*) the reaction was carried out in aqueous acetic acid (30% water) and it was found that phenylhydrazine was appreciably acetylated under the conditions used; (*b*) benzoin phenylhydrazone dissolved but slowly in the aqueous acetic acid and a precipitate of benzil bisphenylhydrazone (identified by m. p. and mixed m. p., 241°) was obtained, owing to the fact that benzoin phenylhydrazone co-exists in the solution in equilibrium with benzoin and phenylhydrazine.

The reaction of phenylhydrazine with the aqueous acetic acid was therefore investigated separately and the reaction was found to be of first order, owing to the large excess of acetic acid. In addition, 1-acetyl-2-phenylhydrazine was completely without action on benzoin phenylhydrazone under the same conditions. These results were then used to calculate the amount of phenylhydrazine consumed by acetylation during the reaction with benzoin phenylhydrazone. The amount of phenylhydrazine consumed in osazone formation (denoted by *P*) was taken to be the difference between the total amount of phenylhydrazine consumed and that consumed by acetylation. *P* is obviously too small as no account has been taken of the phenylhydrazine that is present

in the medium owing to the reversible dissociation of the hydrazone. In addition, the amount of phenylhydrazine consumed by acetylation has been calculated without consideration of the simultaneous reaction to form osazone, so that its value is slightly large.

Despite the fact that *P* is too small, the value of the ratio between *P* and ammonia formed exceeds 2 initially in all the reactions investigated. It then falls below 2 and finally begins to approach 2 again (see Table 3). These results are not in accord with mechanism (I), and so mechanism (II) is favoured. The values much greater than 2 are obtained after short reaction times during which it is assumed that the equilibrium

$$Ph{\cdot}NH{\cdot}N{:}CPh{\cdot}CHPh{\cdot}OH + H_2O \rightleftharpoons O{:}CPh{\cdot}CHPh{\cdot}OH + Ph{\cdot}NH{\cdot}NH_2$$

has not been established. As the reaction proceeds, the phenylhydrazine thus produced causes the value to fall below 2, but its effect will be less marked as the reaction proceeds and the value of the ratio should once again approach 2.

When benzoin phenylhydrazone alone was allowed to react with the aqueous acetic acid at 49·1°, it was found that 0·273 mole of ammonia per mole of hydrazone was formed at infinite time. Benzil bisphenylhydrazone was also isolated (see above). If the reaction involved is assumed to be

$$3Ph{\cdot}NH{\cdot}N{:}CPh{\cdot}CHPh{\cdot}OH + H_2O \longrightarrow Ph{\cdot}NH{\cdot}N{:}CPh{\cdot}CPh{:}N{\cdot}NHPh + 2O{:}CPh{\cdot}CHPh{\cdot}OH + Ph{\cdot}NH_2 + NH_3$$

then 0·333 mole of ammonia per mole of hydrazone should be produced. This difference (0·060 mole of ammonia) may be ascribed to the amount of phenylhydrazine lost by acetylation. Fortunately, 1-acetyl-2-phenylhydrazine can be separated quantitatively from a synthetic mixture with benzoin and benzil bisphenylhydrazone owing to its solubility in warm water. In the above reaction it was found that 0·108 mole of 1-acetyl-2-phenylhydrazine per mole of benzoin phenylhydrazone was formed. This corresponds to a decrease of 0·036 mole of ammonia below that expected from the above equation (viz., 0·297 mole), in good agreement with the experimental value (0·273 mole). By contrast, Theilacker and Tröster (*Annalen*, 1951, **572**, 114) found that benzoin phenylhydrazone reacted as follows :

$$HO{\cdot}CHPh{\cdot}CPh{:}N{\cdot}NHPh + H_2O \longrightarrow \underset{(74\%)}{O{:}CPh{\cdot}CPh{:}O} + \underset{(52\%)}{Ph{\cdot}NH_2} + NH_3$$

It should be noted, however, that these authors used aqueous acetic acid at 100°. On the other hand, benzil monophenylhydrazone was quantitatively recovered unchanged, under our conditions, in agreement with Theilacker and Tröster.

The reaction of phenylhydrazine with benzoin was also investigated at 39·7°, and it was found that the rates of production of ammonia and aniline were almost identical, which supports stage (*F*).

Experimental

Benzoin.—Commercial benzoin was crystallised four times from absolute alcohol (twice with charcoal), giving cream-coloured needles, m. p. **134—136°**.

Benzoin Phenylhydrazone.—Benzoin (3·0 g., 0·014 mole) was heated with pure phenylhydrazine (1·5 g., 0·014 mole) on the water-bath until all the benzoin had dissolved. Alcohol was added and the product allowed to crystallise. The benzoin phenylhydrazone was then recrystallised from absolute alcohol, giving colourless needles, m. p. 106°. Smith (*Amer. Chem. J.*, 1899, **22**, 199) gives m. p. 106°.

Acetic Acid.—Excess of liquid was removed from crystalline acetic acid which was then refluxed (3 hours) with chromium trioxide (1·5% by wt.), and the product distilled twice. Water (*ca.* 30% by wt.) was added until the d^{20} was 1·070.

Phenylhydrazine.—Commercial phenylhydrazine was distilled *in vacuo*, and the distillate frozen at 7°. The oily portion was then decanted and the residue redistilled, the constant-boiling fraction being reserved. Owing to the difficulty of preventing aerial oxidation, it was

converted into its hydrochloride, which is quite stable (cf. Ardagh, Kellam, Rutherford, and Walstaff, *loc. cit.*). The product was free from ammonium chloride.

Procedure.—Benzoin phenylhydrazone was dissolved in 30% aqueous acetic acid (*ca.* 25—30 ml.), at the temperature of the bath, in a 50-ml. flask. Phenylhydrazine hydrochloride and the exact amount of 1·000N-sodium hydroxide required to neutralise the phenylhydrazine hydrochloride were then added and the solution made up to the mark with the aqueous acetic acid. At determined times, 5-ml. aliquots were withdrawn, added to 5 ml. of 0·5N-hydrochloric acid, and extracted with ether. The ethereal layer was then well washed with distilled water, and the washings were added to the aqueous extract. The aqueous layer was then analysed as follows: Ammonium ion was determined by the use of a standard micro-Kjeldahl apparatus (phenolphthalein); separate experiments showed that the addition of aniline and phenylhydrazine did not interfere. Phenylhydrazine present was determined by Ardagh and Williams's iodometric method (*J. Amer. Chem. Soc.*, 1925, **47**, 2976); addition of aniline and

TABLE 1.

Wt. of $Ph{\cdot}NH{\cdot}NH_2,HCl$ = 0·4281 g. (29·67 × 10^{-4} mole). Concn. of $CH_3{\cdot}CO_2H$ = 12·31 mole $l.^{-1}$ (const.). Temp. = 59·7°.

Time (min.)		150	250	350	450	550
$Ph{\cdot}NH{\cdot}NH_2$ consumed (10^{-4} mole)	obs.	7·40	10·74	13·60	16·40	18·80
	calc.	7·10	10·43	14·00	16·61	18·80

$k = 2{\cdot}47 \times 10^{-6}$ $mole^{-1}$ l. $sec.^{-1}$.

TABLE 2.

Temp.:	39·7°	49·1°	59·7°
10^7k ($mole^{-1}$ l. $sec.^{-1}$)	1·83, 2·06, 1·85	7·04, 6·96, 6·88	23·4, 24·7, 23·8
(Average)	1·91	6·96	24·0

The bimolecular constants obey the Arrhenius equation as shown by the following data, where the calculated values are given by $k = 8{\cdot}70 \times 10^{11}e^{-26,600/RT}$.

Temp.:		39·7°	49·1°	59·7°
10^7k	obs.	1·91	6·96	24·0
	calc.	1·95	6·75	25·1

TABLE 3. *Reaction of phenylhydrazine with benzoin phenylhydrazone.*

Wt. of $Ph{\cdot}NH{\cdot}NH_2,HCl$ = 0·2882 g. (19·94 × 10^{-4} mole).
Wt. of benzoin phenylhydrazone = 0·2716 g. (8·99 × 10^{-4} mole).

Temp.	Time (min.)	NH_3 formed (10^{-4} mole)	Total $Ph{\cdot}NH{\cdot}NH_2$ used (10^{-4} mole)	$Ph{\cdot}NH{\cdot}NH_2$ used by acetylation (× 10^{-4} mole)	P (× 10^{-4} mole)	P/NH_3 formed
39·7°	100	1·39	3·87	0·23	3·64	2·62
	200	2·48	4·77	0·48	4·29	1·73
	500	3·71	7·07	1·05	6·02	1·62
	1000	4·72	10·01	1·90	8·11	1·72
	1600	5·30	12·55	2·62	9·93	1·87
	3100	5·96	15·00	3·67	11·33	1·90
49·1	100	1·69	5·12	0·88	4·24	2·50
	200	2·70	7·37	1·47	5·90	2·18
	300	3·36	8·99	2·07	6·92	2·06
	400	3·78	10·14	2·67	7·47	1·98
	500	4·12	11·13	3·08	8·05	1·96
	∞	4·58	—	—	—	—
59·7	100	3·09	9·06	2·65	6·41	2·07
	200	3·77	11·03	4·38	6·65	1·76
	300	3·90	12·83	5·88	6·95	1·78
	400	4·04	14·48	6·92	7·56	1·87
	∞	4·60	—	—	—	—

TABLE 4. *Reaction of phenylhydrazine with benzoin.*

Wt. of $Ph{\cdot}NH{\cdot}NH_2,HCl$ = 0·4275 g. (29·59 × 10^{-4} mole).
Wt. of benzoin = 0·1905 g. (8·99 × 10^{-4} mole). Temp. = 39·7°.

t (min.)	200	400	1000	1400	2000
NH_3 formed (10^{-4} mole)	2·48	3·28	4·72	5·12	5·49
$Ph{\cdot}NH_2$ formed (10^{-4} mole)	2·44	3·17	4·52	5·07	5·35

ammonium ion was independently found to have no effect on this estimation. Aniline was determined by prior destruction of the phenylhydrazine with a warm aqueous acetic acid solution of cupric sulphate, and titration with bromine solution by Pamfilov's method (*Ind. Eng. Chem.*, **1926**, **18**, 763); methyl-red was a better indicator than indigo-carmine; ammonium ion did not interfere.

The acetylation of phenylhydrazine and also its reaction with benzoin were also measured. All the reactions were performed in a stream of nitrogen.

The results (all obtained in duplicate) are shown in the following tables. The temperatures were accurate to $\pm 0{\cdot}1°$.

Reaction of Phenylhydrazine with 30% *Aqueous Acetic Acid.*—A typical example is given in Table 1. Results are summarised in Table 2.

We thank Drs. N. V. Riggs and C. C. J. Culvenor for helpful discussion.

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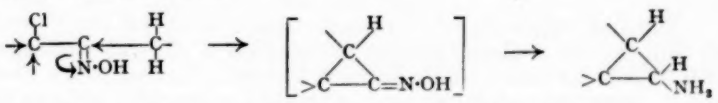
[*Received, October 15th*, 1951.]

120. *The Chemistry of Humulene. Part II.**

By G. R. CLEMO and J. O. HARRIS.

The infra-red absorption spectra of some humulene derivatives have been determined. The vigorous oxidation of dihydrohumulene has yielded *as*-dimethylsuccinic acid and ββ-dimethyladipic acid. Ozonolysis of tetrahydrohumulene has given a C_{15} dicarboxylic acid, the thorium salt of which cannot be ketonized. Considerations of this physical and chemical information, together with the newer structures for β-caryophyllene advanced by Šorm *et al.* (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) and Dawson, Ramage, and Wilson (*Chem. and Ind.*, **1951**, **464**) suggest a provisional structure for humulene as 1 : 4 : 4 : 8-tetramethyl*cyclo*undeca-1 : 5 : 8-triene. The various transformations involved in these degradations are discussed.

THE investigation of the structure of the monocyclic triene sesquiterpene hydrocarbon humulene (α-caryophyllene) which we have shown to be identical with didymocarpene from *Didymocarpus pedicillata* (Clemo and Harris, *J.*, 1951, 22) has been continued. In that communication we described the preparation of α- and β-aminotetrahydrohumulene by hydrogenation of humulene nitrosochloride over Raney nickel at 100°/100 atm., and their further reduction with hydrogen over Adams's platinum oxide in acetic acid to aminohexahydrohumulenes. The decomposition of the corresponding α- and β-dimethylaminotetrahydrohumulene methiodides under Hofmann conditions yielded α- and β-dihydrohumulene, both of which would absorb two further molecules of hydrogen; the presence of two ethylenic linkages in the α-hydrocarbon has been confirmed by titration with perbenzoic acid. It was thought at first that in the tetrahydro-amine series both α- and β-compounds—these being most simply considered to be stereo-isomeric forms—contained a double bond which was difficult to hydrogenate, but after attempts to oxidize the highly crystalline α-acetamidotetrahydrohumulene with potassium permanganate in acetone, or with perbenzoic acid in chloroform, only unchanged material was identifiable. The α- and β-tetrahydro-amines therefore probably contain *cyclo*propane structures, which may arise by 1 : 3-dehydrohalogenation between a tertiary halide and a methylene group, activated by an α-nitroso- or hydroxyimino-structure, in the presence of the alkaline catalyst prior to reduction, thus :



Infra-red absorption spectra measurements on α-aminotetrahydrohumulene (Fig. 1) confirm this view, since this compound possesses an absorption band at 1020 cm.$^{-1}$, the fre-

* Part I, Clemo and Harris, *J.*, 1951, 22.

quency associated with the *cyclo*propane structure (Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482). The presence in this spectrum of an absorption band at 970 cm.$^{-1}$ could be taken as indicative of the presence of the R·CH=CH·R group (see below), but it is difficult to reconcile a structure containing this group with the stability under the above conditions of oxidation and reduction. The 1020- and 970-cm.$^{-1}$ bands disappear on hydrogenation, as illustrated by the spectrum of aminohexahydrohumulene (Fig. 2).

The infra-red absorption spectra of α-dihydro-, tetrahydro-, and hexahydro-humulene,

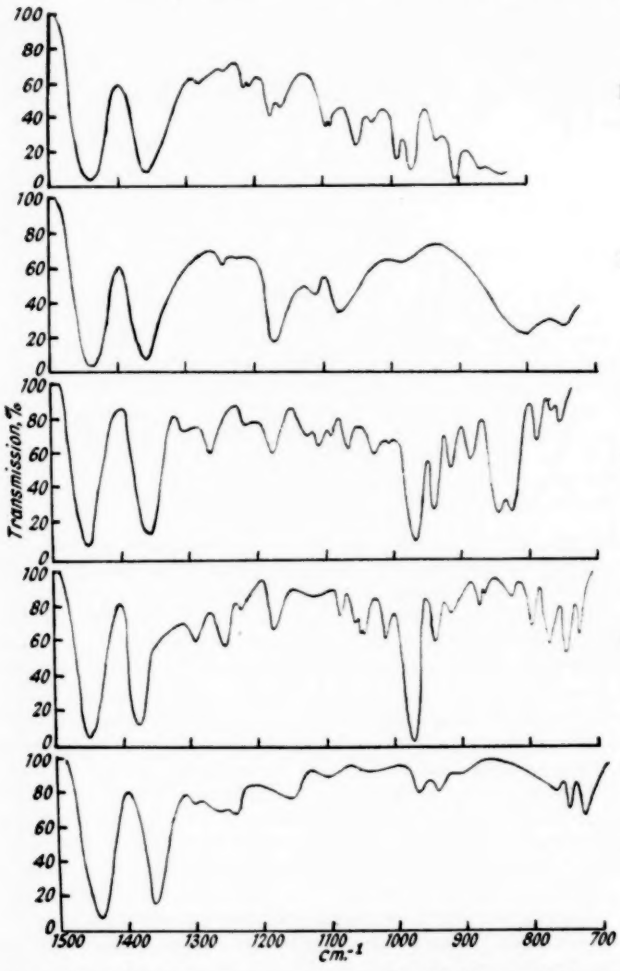


FIG. 1. *Aminotetrahydrohumulene.*

FIG. 2. *Aminohexahydrohumulene.*

FIG. 3. *Dihydrohumulene.*

FIG. 4. *Tetrahydrohumulene.*

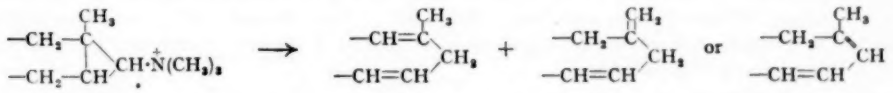
FIG. 5. *Hexahydrohumulene.*

all of which have been prepared from the highly purified crystalline parent α-aminotetrahydrohumulene hydrochloride, have also been measured (Figs. 3—5). The doubly unsaturated α-dihydrohumulene shows a marked absorption at 967 cm.$^{-1}$, which may be associated with the out-of-plane hydrogen deformation of the *trans*-arrangement of the group R·CH=CH·R (for references see Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915), while the band in the 12-μ region with peaks at 840 and 831 cm.$^{-1}$ suggests the presence of two arrangements of the group R·CH=CR′R″. The smaller absorption at 885 cm.$^{-1}$ in this substance could be associated with a third type of olefinic unsaturation, *viz.*, CH_2=CRR′, suggesting that this substance is, in fact, a mixture of

hydrocarbons. Our inability to isolate a crystalline adduct with maleic anhydride suggests that there is no conjugation, but as we postulate a possible large-ring diene structure for these substances (see below) this may not be conclusive: evidence obtained on Stuart models indicates that such Diels–Alder adducts would be considerably strained. The recent observations that *cyclo*octa-1:3-diene does not form a simple adduct (Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128; Zeigler and Wilms, *Annalen*, 1950, **567**, 1) emphasise that conjugation in α-dihydrohumulene and presumably, therefore, in the parent humulene cannot be entirely excluded.

Ultra-violet absorption measurements show only end absorption below 2350 Å, but the observations by Pesch and Friess (*J. Amer. Chem. Soc.*, 1950, **72**, 5756) that absorption of cyclic conjugated dienes varies with ring size, and lack of information above *cyclo*octadiene make any decision on this evidence also difficult.

Such a mixture of dienes could be envisaged to arise contemporaneously with the opening of a *cyclo*propane ring in the following manner:

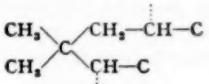


The infra-red absorption spectrum of the more highly reduced tetrahydrohumulene does not possess the marked unsaturation bands at 12 or 11·3 μ present in α-dihydrohumulene, but still retains the absorption associated with *trans*-R·CH=CH·R at 967 cm.$^{-1}$. All the spectra show the characteristic frequency due to the methyl (1360 cm.$^{-1}$) and saturated methylene group (1450 cm.$^{-1}$). The three bands determined in the spectra of tetrahydro- and hexahydro-humulenes between 770 and 720 cm.$^{-1}$ can be associated with rocking vibrations of different CH_2 groups (Shephard and Sutherland, *Nature*, 1947, **159**, 739; Szasz, Shephard, and Rank, *J. Chem. Phys.*, 1948, **16**, 704; Rasmussen, *ibid.*, p. 712; Barrow, *ibid.*, 1951, **19**, 345).

Further evidence of the structure has been obtained by chemical investigation. Vigorous oxidation of β-dihydrohumulene with potassium permanganate in acetone at 30°, followed by 50% nitric acid on the water-bath, in sufficient quantity to permit close fractionation of the methyl esters of the acid fraction, followed by chromatographic purification of the free acids, has yielded so far two solid acids, namely, *as*-dimethylsuccinic acid (thus confirming the presence of a *gem*-dimethyl group in the molecule) and ββ-dimethyladipic acid.

Tetrahydrohumulene has been obtained from α-dimethylaminohexahydrohumulene by quaternization and subsequent Hofmann decomposition (Clemo and Harris, *loc. cit.*); this tertiary base may be prepared either by direct reduction over platinum in acetic acid of α-dimethylaminohumulene or of α-aminotetrahydrohumulene with subsequent methylation of the resulting primary base. The products are identical as shown by the identity of the methiodides, but the reduction of the primary base proceeds much more rapidly. The presence of the R·CH=CH·R group in tetrahydrohumulene is confirmed as an endocyclic double bond since ozonolysis yields a C_{15} dicarboxylic acid. This acid is contaminated with a small amount of material which yields iodoform with sodium hypoiodite, but the absence of ketonic derivatives, an equivalent weight determination, and analysis of derivatives together with the above infra-red data suggest strongly that this material is adventitious. The acid on distillation with acetic anhydride gives an anhydride, and dry distillation of the thorium salt has not yielded any identifiable ketonic material.

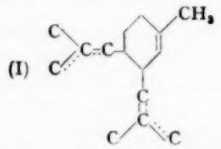
This last observation was considered at first to be indicative of the presence of a four- or a five-membered ring system in tetrahydrohumulene (*cf.* Clemo and Harris, *Chem. and Ind.*, 1951, 50). However, the ββ-dimethyladipic acid can only arise from the system:

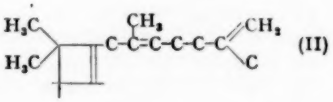


If it is assumed that the *gem*-dimethyl group is in a ring it is not feasible to accommodate this structure in less than a six-membered ring if it is to yield the above acid on oxidation.

The presence of a six-membered ring is difficult to reconcile with our inability to ketonize the thorium salt of the C_{15} acid. Also the infra-red spectrum of hexahydrohumulene would not appear to support a *cyclo*hexane system as the absorption at 967 cm.$^{-1}$ does not have a corresponding band between 1000 and 1055 cm.$^{-1}$ usually associated with this structure (cf. Marrison, *J.*, 1951, 1614); nevertheless, at present we would not preclude absolutely the possibility on this evidence.

The foregoing experimental data cannot be accommodated on either of the formulæ so far presented for humulene. Structure (I) (Wolfrom and Mishkin, *J. Amer. Chem. Soc.*, 1950, **72**, 5350) does not contain a *gem*-dimethyl group and is derived from an obsolete formula for β-caryophyllene, and structure (II) (Klein and Lahey, *Chem. and Ind.*, 1951, 761) whilst attractive on biogenetic grounds, being directly derivable from the structure (III) proposed by Šorm, Dolyš, and Plíva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) for β-caryophyllene, cannot arise from the more recent modifications (IV) proposed by Dawson, Ramage, and Wilson (*Chem. and Ind.*, 1951, 464). Also, formula (II) does not account for the formation of ββ-dimethyladipic acid, or permit 1 : 3-dehydrohalogenation during reduction of the nitrosochloride.

(I) 


(II)

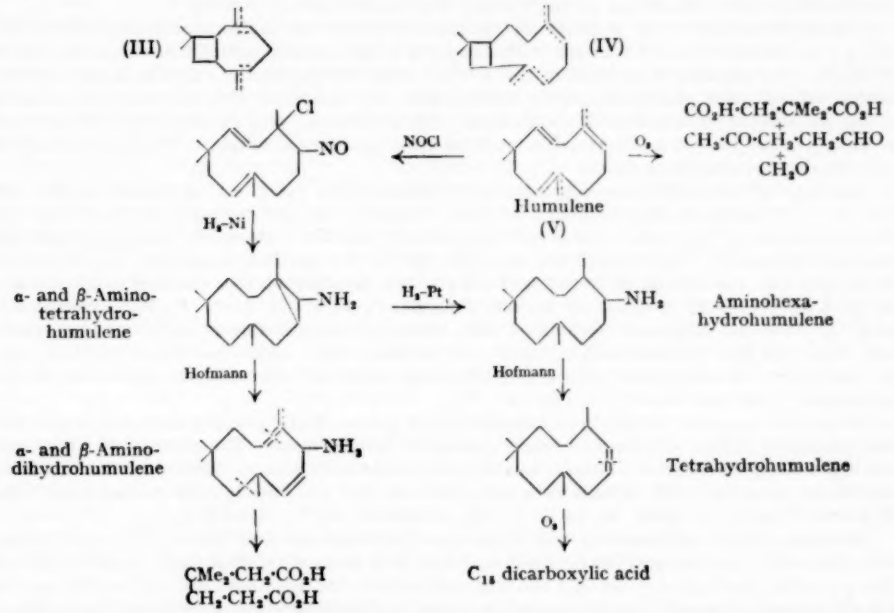
We are aware that several interpretations, which can be further complicated by potential intramolecular rearrangements, are feasible on the evidence under discussion. The possibility of such rearrangements, however, is limited since the infra-red spectrum of hexahydrohumulene prepared by the direct reduction of humulene (Šorm *et al.*, *Coll. Czech. Chem. Comm.*, 1949, **14**, 691) is very similar to that determined above. However, one novel structure (V) for humulene presents itself which may also be considered to have some support on biosynthetic grounds. This eleven-membered ring formula is directly derivable by fission of the four-membered ring, from either structure (III) or the modification (IV) of this *bicyclo*[7 : 2 : 0]undecane ring system. The major transformations encountered are envisaged to occur as shown in the scheme; the C_{15} dicarboxylic acid, now formulated as a tetramethylnonane-1 : 9-dicarboxylic acid, could be expected to undergo ketonization only with difficulty (cf. Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 670, 686; Prelog, *J.*, 1950, 420), although it should readily form an anhydride (cf. Adams and Anderson, *J. Amer. Chem. Soc.*, 1951, **73**, 136).

The large ring also accommodates the *trans*-arrangement of the R·CH=CH·R band indicated by the infra-red absorption spectra (see above) of both dihydro- and tetrahydrohumulene, although variations of this characteristic olefinic band have not yet been correlated with the R·CH=CH·R band deformation in ring structures. However, if all the above assumptions are correct the frequency at 840 cm.$^{-1}$ would be associated with an endocyclic R·CH=CR′R″ group, and Plíva and Herout (*Coll. Czech. Chem. Comm.*, 1950, **15**, 160) have pointed out that when such a structure is associated with a five- or a six-membered ring this value is shifted to higher frequencies, hence the smaller value encountered here might be considered to support the hypothesis of a larger ring.

The 1 : 5 : 8-endocyclic arrangement of the double bonds would be unique in accounting for the formation of *as*-dimethylsuccinic acid and lævulaldehyde as primary oxidation products, and in this case conjugation in the parent hydrocarbon is excluded. However, it should be noted that Šorm *et al.* (*ibid.*, 1949, **14**, 699) did not identify lævulaldehyde as a product of ozonolysis of highly purified humulene and further investigation in this connection is desirable.* A proportion of an isomer with an exocyclic methylene group would account for the formation of formaldehyde on ozonolysis.

* See addendum.

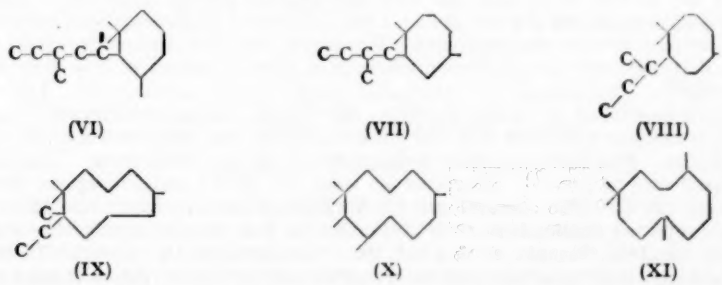
Support for the presence of the three different classes of double bonds, *viz.*, R·CH=CH·R', (*trans*-)RR'C=CH·R'', and RR'C=CH_2, required on this formulation is given in the infra-red spectrum of pure humulene recorded by Plíva and Šorm (*ibid.*, p. 274) which has maxima at 970, 825—830, and 890 cm.$^{-1}$ associated respectively with these olefinic types.



The Stuart model of this optically inactive " head-to-tail isoprenic " alkyl *cyclo*undecatriene has a compact strainless structure.

[*Addendum, October 30th*, 1951.] We have now identified lævulaldehyde as an ozonolysis product of humulene (n_D^{17} 1·5063, *d* 0·8920, $[\alpha]_D^{17}$ +0·39°) purified by chromatography.

On the assumption that humulene arises by a simple coiling of the farnesene chain, contains a cyclic *gem*-dimethyl group, and is a single substance or mixture of closely related isomers differing only by an endo–exo-cyclic bond arrangement, examination of the possible monocyclic carbon skeletons (VI)—(XI) with ring size greater than six shows that only a



structure based on (XI) can accommodate the formation of *as*-dimethylsuccinic acid and lævulaldehyde as primary fission products. In this connection Šorm and Dolejš (*ibid.*, 1950, **15**, 96) have recently shown that a structure derived from (VI) is not possible for humulene.

Experimental

All the infra-red spectra were measured on a Grubb-Parsons single-beam spectrometer, with a variable slit opening (2—6 cm.$^{-1}$ at 6·5—14 μ). The liquid samples were studied as films of 0·05 mm. thickness between sodium chloride plates.

α-Dihydrohumulene (Clemo and Harris, *loc. cit.*) was titrated in chloroform with perbenzoic acid, duplicate determinations giving 2·05 and 2·2 double bonds per mole.

Attempted Oxidation of α-Acetamidotetrahydrohumulene.—α-Acetamidotetrahydrohumulene (0·1 g.) in acetone (15 c.c.) was left with excess of finely ground potassium permanganate for 24 hours. Filtration and removal of the solvent, after the passage of sulphur dioxide, gave a residue which, after chromatographic purification, was identical with the starting material. A similar attempt to oxidize this substance with perbenzoic acid in chloroform in the cold overnight again yielded as identifiable material only the original amide. This substance gives no colour with tetranitromethane.

Aminohexahydrohumulene.—α-Aminotetrahydrohumulene (10·3 g.) in glacial acetic acid (150 c.c.) was shaken with hydrogen at room temperature and pressure for 24 hours over platinum oxide (1·1 g.), after which reduction ceased and the theoretical amount of hydrogen had been absorbed. The solvent was removed, the residue basified, extracted with ether, and dried (Na_2SO_4), the solvent removed, and the residual *hexahydro-amine* distilled as a colourless oil (10·2 g.), b. p. 82°/2 mm., n_D^{22} 1·4813 (Found: C, 79·8; H, 13·7. $C_{15}H_{31}N$ requires C, 80·0; H, 13·8%). This was methylated with formaldehyde and formic acid, and the tertiary base converted into the methiodide, which, recrystallised from water, had m. p. 164° (decomp.) not depressed by admixture with the methiodide prepared from dimethylaminohexahydrohumulene (Clemo and Harris, *loc. cit.*).

Hexahydrohumulene.—Tetrahydrohumulene (0·6 g.) was hydrogenated in glacial acetic acid over platinum oxide. Hydrogen uptake ceased at 1 mole/mole. The solvent was removed, and the residue, in ethereal solution, washed with sodium carbonate, dilute acid, water, dried, and finally distilled from sodium as a colourless oil (0·5 g.), 70—75° (bath-temp.)/0·1 mm., n_D^{24} 1·4714 (Found: C, 85·9; H, 14·2. $C_{15}H_{30}$ requires C, 85·7; H, 14·3%).

Oxidation of Dihydrohumulene with Potassium Permanganate and Nitric Acid.—β-Dihydrohumulene (50 g.) in acetone (750 c.c.) was oxidised with finely divided potassium permanganate (200 g.) added during 2 days so that the temperature did not rise above 30°. The mixture was filtered, the manganese dioxide extracted five times with boiling water, and the aqueous extract combined with the residue obtained from the acetone filtrate by removal of solvent. The whole was made alkaline to phenolphthalein and extracted with ether. The aqueous layer was acidified and repeatedly extracted with ether, the ethereal solution was dried (Na_2SO_4), and the solvent removed. The acid residue was further oxidized by the cautious addition of nitric acid (200 c.c.; *d* 1·23), heating overnight on the water-bath, and concentration in an evaporating basin until no appreciable amount of mineral acid remained. The residue was dissolved in ether and treated with an excess of diazomethane, and the mixed esters were distilled into two main fractions, (A) (20 g.) b. p. 110°/0·1 mm., and (B) (8 g.) b. p. 110—140°/0·1—0·3 mm. Distillate (A) was refractionated in a 6" I.C.I. (Dixon) precision column; it distilled continuously from 90° to 170° at 13 mm., the only approximate plateau being at *ca.* 126°/13 mm. A fraction boiling at 89—94°/13 mm. (0·65 g.) was hydrolysed with methanolic potassium hydroxide and the acid fraction was separated. This slowly solidified, and recrystallised from light petroleum (b. p. 60—80°) as colourless crystals, m. p. alone or mixed with *as*-dimethylsuccinic acid, 138—139°.

The above fraction of (A) boiling at 125·5—127°/13 mm. (2·0 g.) was refluxed with methanol (6 c.c.) and potassium hydroxide (2 g.) for 3 hours, and the free acid distilled at 75—95° (bath-temp.)/0·01 mm. This partly solidified during three weeks in a refrigerator. The solid (0·1 g.) was separated and purified by adsorption on silica gel (10 g.) and subsequent elution with benzene–ether (7 : 3). This chromatographic purification was repeated three times and was followed by repeated sublimation at 70°/0·1 mm. In this manner a colourless solid, m. p. 85—86°, was obtained (Found: C, 55·4; H, 8·0. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·05%).

When warmed with resorcinol and concentrated sulphuric acid, this acid gave a reddish-brown solution, which on dilution and treatment with alkali became deep crimson with a violet fluorescence. The colour was discharged by acid, but returned on basification (cf. Crossley and Renouf, *J.*, 1906, 1552). The m. p. of this acid was depressed on admixture with α-*iso*propylglutaric, αα'-trimethylglutaric, αββ-trimethylglutaric, β-methyl-β-ethylglutaric, αα-dimethyladipic, or *cis*- or *trans*-caryophyllenic acid, but not with ββ-dimethyladipic acid.

The acids other than *cis*- and *trans*-caryophyllenic acids (for these we are gratefully indebted to Dr. G. R. Ramage) were prepared by the recorded methods, except ββ-dimethyladipic acid, which was obtained from ββ-dimethylglutaric acid anhydride as follows: The anhydride (10 g.) was refluxed with methanol (5·5 c.c.) for 2 hours, and the acid-soluble portion separated and distilled, giving methyl hydrogen ββ-dimethylglutarate as a colourless oil (8·5 g.; b. p. 85°/0·3 mm.), which with thionyl chloride at 60° (1 hour) gave monomethyl ester chloride (7·5 g.; b. p. 45°/0·2 mm.). This ester acid chloride (7·5 g.) was added to an excess of diazomethane in ether, and the diazo-ketone which remained after removal of the solvent was treated in methyl-alcoholic solution at 60° with silver oxide (0·2 g.), added during 1 hour in small portions. The reaction was completed on the water-bath. The crude methyl ester was isolated, distilled (5·0 g.; b. p. 58°), and hydrolysed with alcoholic potassium hydroxide, and the crude acid recrystallised from concentrated hydrochloric acid, forming colourless needles (4·2 g.; m. p. 86°) (Found: C, 54·9; H, 7·9%).

Ozonolysis of Tetrahydrohumulene.—Tetrahydrohumulene (2·3 g.) was dissolved in hexane, and ozone was passed in at −80° until the solution became blue. The solution was allowed to come to room temperature, the hexane decanted, the remaining solvent allowed to evaporate, and the residual oily ozonide heated in acetic acid (25 c.c.) on the water-bath overnight. The solvent was removed in a vacuum, the distillate on dilution giving no precipitate with Brady's reagent. The residue was extracted with sodium hydroxide solution and ether. The aqueous fraction was acidified and extracted with ether, and the dried ethereal solution treated with excess of diazomethane. The ester was distilled and the bulk collected at 120°/0·3 mm. (Found: C, 68·2; H, 10·5; ester OMe, 21·0. Calc. for $C_{17}H_{32}O_4$: C, 68·0; H, 10·7%; ester OMe, 21·0%). It was hydrolysed with methanolic potassium hydroxide, and the crude acid (1·3 g.) (Found: equiv., 143) isolated. This was dissolved in cold alkali, treated with excess of iodine, and left overnight, and a small amount of iodoform (0·1 g.; m. p. 119°) was removed. The filtrate was saturated with sulphur dioxide and extracted with ether, and the crude acid slowly heated in a retort with acetic anhydride to 150°. The residue was distilled in a high vacuum (bath-temp., 180°/0·1 mm.). The non-solidifying oily distillate gave no ketonic reactions and was insoluble in sodium carbonate, but dissolved in warm aqueous sodium hydroxide. The acid recovered from this solution was redistilled in a high vacuum (bath-temp., 80—90°/0·1 mm.) and obtained as an oil (Found: C, 66·4; H, 10·0%; equiv., 140. Calc. for $C_{15}H_{28}O_4$: C, 66·2; H, 10·3%; equiv., 136).

The *di*-p-*bromophenylthiuronium* salt was prepared by treating the neutral solution with two equivalents of *p*-bromophenylthiuronium bromide in alcohol and crystallized from acetone as clusters of feathery needles, m. p. 160·5° (Found: C, 49·1; H, 6·0. $C_{31}H_{46}O_4N_4Br_2S_2$ requires C, 48·8; H, 6·0%).

The thorium salt (0·75 g.), prepared by addition of thorium nitrate to a neutral solution of the acid in aqueous ammonia, yielded on dry distillation up to 320° under reduced pressure (water-pump) a trace of distillate which gave no ketonic reactions.

The authors thank Messrs. White, Tompkins, and Courage, Ltd., and Monsanto Chemicals Ltd., for generous samples of hop oil residues and clove oil terpenes respectively.

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[*Received, October 2nd,* 1951.]

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121. *Synthetic Long-chain Aliphatic Compounds. Part VII.* Some Mono-olefinic Acids.*

By (MISS) B. W. BOUGHTON, R. E. BOWMAN, and (in part) D. E. AMES.

By the acyloin route (*J.*, 1951, 1079) the pure *cis*- and *trans*-forms of myristoleic, palmitoleic, and gadoleic acids have been obtained. The *cis*- and the *trans*-isomer of octadec-4-enoic acid † have been prepared by the methoxy-ketone route (*loc. cit.*), attempts to use the other route having failed.

IN Part III of this series (*J.*, 1951, 1079), we described a method of olefinic acid synthesis, in which acyloins (I; R′ = H) are first reduced to the corresponding dihydroxy-acids which are then separated by fractional crystallisation into the *erythro*- and *threo*-isomers. The

* Part VI, *J.*, 1951, 2752. † Geneva nomenclature (CO_2H = 1), throughout.

latter on separate treatment with hydrogen bromide–acetic acid–sulphuric acid, followed by zinc, furnished the individual *cis*- and *trans*-unsaturated acids respectively as follows :

$$\underset{\text{(I)}}{R{\cdot}CH(OR'){\cdot}CO{\cdot}[CH_2]_n{\cdot}CO_2H} \longrightarrow \underset{\text{(II)}}{R{\cdot}CH(OR'){\cdot}CH(OH){\cdot}[CH_2]_n{\cdot}CO_2H} \longrightarrow$$

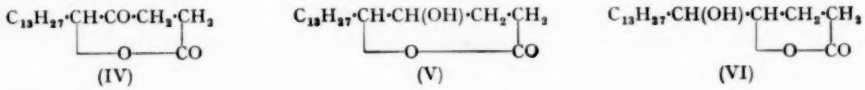
$$R{\cdot}CHBr{\cdot}CHBr{\cdot}[CH_2]_n{\cdot}CO_2H \longrightarrow R{\cdot}CH{:}CH{\cdot}[CH_2]_n{\cdot}CO_2H \quad \text{(III)}$$

It was considered that *cis*- and *trans*-heptadec-9-enoic acids prepared in this manner were of a high degree of purity and we now report three more examples of this synthesis which, it is thought, provide further evidence of the high purity of unsaturated acids obtained by this method.

First, starting from 2-hydroxyhexanoic acid † and triethyl heptane-1 : 1 : 7-tricarboxylate, we obtained by means of the debenzylation–ketone synthesis (Bowman, *J.*, 1950, 325) the acyloin (I; $R = CH_3{\cdot}[CH_2]_3$, $R' = H$, $n = 7$) which was reduced catalytically; the *erythro*- and *threo*-9 : 10-dihydroxytetradecanoic acids were separated by crystallisation. The separate isomers were then converted into their dibromides which on debromination with zinc furnished *cis*- and *trans*-myristoleic acids (tetradec-9-enoic acids), m. p. −4·5° to −4°, and 18—18·5° respectively. Similarly from 2-hydroxyoctanoic and 2-hydroxydodecanoic acids, *cis*- and *trans*-palmitoleic acids (hexadec-9-enoic acids) of m. p. 0—0·5° and 31—32° respectively, and *cis*- and *trans*-gadoleic acids (eicos-9-enoic acids) m. p. 23—23·5° and 54° respectively were obtained, all of a high degree of purity as judged by the narrow ranges of their melting points and those of their derivatives and by their excellent iodine values.

Attention was next directed to the synthesis of the octadec-4-enoic acids using the same route. The necessary starting material, 2-hydroxypentadecanoic acid, was obtained by a six-stage synthesis from pure lauryl alcohol and was converted by successive treatment with acetyl and thionyl chlorides into the corresponding acetoxy-chloride which was treated with tribenzyl sodioethane-1 : 1 : 2-tricarboxylate in the usual manner. The yield of product was, however, very low, the crystalline δ-lactone (IV) (*ca.* 12%) and the ethyl ester of (I; $R = C_{13}H_{27}$, $R' = H$, $n = 2$) (*ca.* 8%) being obtained; the latter could be converted into (IV) by heating it with a catalytic quantity of toluene-*p*-sulphonic acid.

Reduction of (IV) in ethanolic solution using Raney nickel W7 catalyst proceeded readily and yielded one of the isomeric hydroxy-lactones (V) in a pure condition. Evidence for the δ-lactone structure of (V) was obtained by similar reduction of the ethyl ester of a crude specimen of (I; $R = C_{13}H_{27}$, $R' = H$, $n = 7$) which afforded after hydrolysis and distillation a small quantity of a different crystalline lactone which would undoubtedly be the γ-form (VI) :



(IV) (V) (VI)

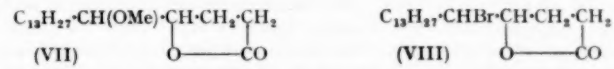
In neither case could the lower-melting isomeric lactone be isolated.

Treatment of (V) with hydrogen bromide–acetic acid–sulphuric acid gave an impure dibromo-acid, converted by zinc under the usual conditions into an olefinic acid, which was obviously a mixture and was obtained in too small a quantity for separation. On account of the low yields obtained with this method and the difficulties associated with later steps, we next investigated our alternative methoxy-ketone route.

The starting material, 2-methoxypentadecanoic acid, was obtained either from the product of interaction of the corresponding bromo-ester with sodium methoxide or by reaction of *n*-tridecyl iodide and sodiomethoxymalonate followed by hydrolysis and decarboxylation in the usual manner. Reaction of this acid and oxalyl chloride gave 2-methoxypentadecanoyl chloride, which on treatment with tribenzyl sodioethane-1 : 1 : 1-tricarboxylate as previously gave, in satisfactory yield, 4-keto-5-methoxyoctadecanoic acid (I; $R = C_{13}H_{27}$, $R' = CH_3$, $n = 2$), isolated as its methyl ester. Catalytic reduction of the ester over Raney nickel W7 furnished, after hydrolysis and distillation, the methoxy-

† See footnote, p. 671.

lactone (VII) in high yield but conversion of this material into the required 4 : 5-dibromo-acids proved more difficult than usual on account of their tendency to pass into the bromo-lactone (VIII).



Thus, reaction of (VII) with hydrogen bromide–acetic acid–sulphuric acid furnished a crude semi-solid dibromo-acid (Found: Br, 33. Calc.: Br, 36%) from which a crystalline 4 : 5-dibromo-octadecanoic acid (presumably the *erythro*-form) was isolated by means of its sparing solubility in light petroleum. Our usual practice at this stage has been to convert the acids into their ethyl esters and to percolate the latter through a short column of alumina to remove traces of colour before distillation but, when these techniques were applied to the petroleum-soluble bromo-compounds, the greater part of the product adhered to the absorbent and could not be eluted. Repeated distillation of the eluates eventually gave a semi-solid mass from which one of the diastereoisomers of (VIII) was obtained in an almost pure state : it appears that loss of elements of ethyl bromide took place before absorption on alumina and also afterwards during distillation ; in the former case the alkalinity of the absorbent was sufficient to hold the product as the alkali salt.

Debromination of the solid dibromo-acid with zinc in methanol furnished pure *trans*-octadec-4-enoic acid whereas, after several trials, it was found that a similar debromination of either the bromo-lactone (VIII) or the mixed crude dibromo-acids gave a mixture of the *cis*- and *trans*-acids from which the individual isomers could be obtained by crystallisation of either their zinc salts or, more conveniently, the free acids themselves.

The *cis*-acid had m. p. 40—41°, and the *trans*-acid m. p. 59·5—60·5°, and both acids gave excellent iodine values (Wijs; 89·4—89·9; Calc.: 89·9). Therefore, the acid of m. p. 52° and iodine value of 27·0 (Hübl) obtained by Eckert and Halla (*Monatsh.*, 1913, **34**, 1821) by a series of operations starting from 2-bromostearic acid was presumably a mixture of the αβ- and γδ-unsaturated acids; our results are in accord with the observations of Linstead and his co-workers (*J.*, 1927, 2565; 1929, 2153) that, while αβ- and βγ-unsaturated acids possess iodine values which are either very low or rather high respectively, those of the γδ-isomers approximate to the theoretical values.

Experimental

Unless otherwise specified, the methods of olefinic acid synthesis were as described in Part III (*loc. cit.*) for the *cis*- and *trans*-heptadec-9-enoic acids, the later stages being detailed in Part IV (*J.*, 1950, 1087).

Light petroleum refers to material of b. p. 40—60°.

cis- *and* trans-*Tetradec-9-enoic Acids.*—2-Hydroxyhexanoic acid (m. p. 62—63°) was converted into *2-acetoxyhexanoyl chloride*, a colourless liquid, b. p. 54°/0·3 mm. (Found: Cl, 18·6. $C_8H_{13}O_3Cl$ requires Cl, 18·4%), and the latter treated with tribenzyl sodio-heptane-1 : 1 : 7-tricarboxylate according to the general method; the product was hydrogenated, decarboxylated, and esterified, to give *ethyl 10-hydroxy-9-ketotetradecanoate* as a pale yellow oil, b. p. 144—150°/0·1—0·3 mm., n_D^{20} 1·4596 (Found : C, 67·3; H, 9·9. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%).

Reduction over Raney nickel W7, followed by hydrolysis, yielded the mixed hydroxy-acids, which were fractionally crystallised from ethanol and then ethanol–ethyl acetate, to give the less soluble erythro- (rhombic plates from ethanol; m. p. 123—124°) and the more soluble threo-9 : 10-*dihydroxytetradecanoic acid* (prisms from ethyl acetate; m. p. 80°) (Found : C, 65·1; H, 10·8. $C_{14}H_{28}O_4$ requires C, 64·6; H, 10·8%).

Reaction of the former dihydroxy-acid with hydrogen bromide–acetic acid–sulphuric acid gave *ethyl* threo-9 : 10-*dibromotetradecanoate*, b. p. 168°/0·5 mm., n_D^{20} 1·4890 (88%) (Found : C, 46·5; H, 7·0. $C_{16}H_{30}O_2Br_2$ requires C, 46·4; H, 7·3%), converted by zinc into ethyl *cis*-tetradec-9-enoate, b. p. 120°/0·6 mm., n_D^{20} 1·4503 (Found: I.V., 100·0. Calc. for $C_{16}H_{30}O_2$: I.V., 99·8), which on hydrolysis furnished *cis*-tetradec-9-enoic acid, b. p. 144°/0·6 mm., n_D^{20} 1·4563, m. p. (thermometer in liquid) −4·5° to −4° (Found : C, 74·7; H, 11·4%; I.V., 111. Calc. for $C_{14}H_{26}O_2$: C, 74·3; H, 11·5%; I.V., 112). It formed a p-*phenylphenacyl* ester, colourless plates (from light petroleum), m. p. 57—58° (Found: C, 79·5; H, 8·4. $C_{28}H_{36}O_3$ requires C, 80·0; H, 8·6%).

threo-9 : 10-Dihydroxytetradecanoic acid furnished similarly *ethyl* erythro-9 : 10-*dibromotetradecanoate*, b. p. 177°/0·7 mm., n_D^{20} 1·4898 (Found : C, 46·7; H, 7·4%), *ethyl* trans-*tetradec*-9-*enoate*, b. p. 112°/0·4 mm., n_D^{20} 1·4515 (Found : C, 75·8; H, 11·9%; I.V., 98·9. $C_{16}H_{30}O_2$ requires C, 75·6; H, 11·8%; I.V., 99·8), and finally trans-*tetradec*-9-*enoic* acid, plates, m. p. 18—18·5°, from light petroleum at −20° (Found : C, 74·8; H, 11·7%; I.V., 112).

cis- *and* trans-*Hexadec*-9-*enoic Acids*.—The above synthesis was repeated with 2-*acetoxyoctanoyl chloride*, b. p. 69°/0·3 mm. (Found : Cl, 16·3. $C_{10}H_{17}O_2Cl$ requires Cl, 16·1%), in place of the hexanoic derivative, to give *ethyl* 10-*hydroxy*-9-*ketohexadecanoate*, a pale yellow oil, b. p. 160—164°/0·4 mm., n_D^{20} 1·4502 (Found : C, 69·2; H, 10·9. $C_{18}H_{34}O_4$ requires C, 68·8; H, 10·9%). Hydrogenation, followed by hydrolysis and fractional crystallisation from ethanol and then ethanol–ethyl acetate, furnished the less soluble *erythro*- (m. p. 129—130°) and the more soluble *threo*-9 : 10-dihydroxyhexadecanoic acid (m. p. 85—86°).

The former acid was then treated with hydrogen bromide in the usual manner, the crude dibromo-acid was esterified and debrominated, and the product hydrolysed and distilled, giving *cis*-hexadec-9-enoic acid as a colourless oil, b. p. 162°/0·6 mm., m. p. 0—0·5°, n_D^{20} 1·4585 (Found : I.V., 100·5. Calc. for $C_{16}H_{30}O_2$: I.V., 100). It formed a p-*phenylphenacyl* ester, plates (from acetone), m. p. 56·5—57° (Found : C, 80·0; H, 8·7. $C_{30}H_{40}O_3$ requires C, 80·4; H, 8·9%). Baudart (*Compt. rend.*, 1945, **220**, 404) reports m. p. 40—41°, a value which is clearly too low by analogy with the derivatives of homologous acids.

The *threo*-dihydroxy-acid gave, in the same manner, *trans*-hexadec-9-enoic acid, colourless plates, m. p. 31—32°, from light petroleum at −30° (Found : I.V., 100·2). Baudart (*loc. cit.*) reports m. p. 32—33°.

cis- *and* trans-*Eicos*-9-*enoic Acids*.—The starting materials were 2-*acetoxydodecanoyl chloride*, b. p. 125°/0·7 mm. (Found : Cl, 12·9. $C_{14}H_{25}O_3Cl$ requires Cl, 12·8%), and tribenzyl sodioheptane-1 : 1 : 7-tricarboxylate. The crude acyloin-acid remaining after removal of unchanged tricarboxylic acid (see Part III ; *loc. cit.*) was esterified azeotropically with ethanol, and the crude ester hydrogenated over Raney nickel in ethanolic solution until absorption of hydrogen ceased. Hydrolysis of the reduction product furnished the mixed dihydroxy-acids which were separated by crystallisation from methanol, to give the less soluble *erythro*- (plates, m. p. 130—131°) and the more soluble *threo*-9 : 10-dihydroxyeicosanoic acids (rectangular plates, m. p. 97—98°).

The former acid then furnished, as before, *ethyl* threo-9 : 10-*dibromoeicosanoate*, b. p. 222°/0·3 mm. (slight decomp.), n_D^{20} 1·4843 (Found : C, 53·7; H, 8·7. $C_{22}H_{42}O_2Br_2$ requires C, 53·0; H, 8·4%), ethyl *cis*-eicos-9-enoate, b. p. 154—155°/0·1 mm., n_D^{20} 1·4545 (Found : I.V., 74·2. Calc. for $C_{22}H_{42}O_2$: I.V., 75·1), and then *cis*-eicos-9-enoic acid, b. p. 170°/0·1 mm., m. p. 23—23·5° (thermometer in liquid) (Found : C, 77·8; H, 12·2%; I.V., 81·3. Calc. for $C_{20}H_{38}O_2$: C, 77·4; H, 12·3%; I.V., 81·8). This formed a lithium salt, which separated from methanol in plates, m. p. 180°, and a p-*phenylphenacyl* ester, colourless glistening plates (from light petroleum), m. p. 66—66·5° (Found : C, 81·1; H, 9·5. $C_{34}H_{48}O_3$ requires C, 81·0; H, 9·5%).

threo-9 : 10-Dihydroxyeicosanoic acid on treatment with the hydrogen bromide reagent furnished erythro-9 : 10-*dibromoeicosanoic acid* as a solid, which crystallised from light petroleum in colourless prisms, m. p. 56° (Found : C, 51·1; H, 8·0. $C_{20}H_{38}O_2Br_2$ requires C, 51·1; H, 8·1%). The latter was esterified azeotropically, the crude ester debrominated with zinc, and the product hydrolysed, to give trans-*eicos*-9-*enoic acid* as colourless shining plates, m. p. 54°, from methanol (Found : C, 77·5; H, 12·2%; I.V., 80·8. $C_{20}H_{38}O_2$ requires C, 77·4; H, 12·3%; I.V., 81·8). The p-*phenylphenacyl* ester separated as plates, m. p. 75°, from light petroleum (Found : C, 81·0; H, 9·4%).

cis- *and* trans-*Octadec*-4-*enoic Acids*.

(I) *Attempts using the Acyloin Route* (with D. E. Ames).—2-*Acetoxypentadecanoyl chloride*. *n*-Dodecylmagnesium bromide (from *n*-dodecanol, f. p. 23·5°) was treated with formaldehyde following Adams and Noller (*Org. Synth.*, 1926, **6**, 22), to give *n*-tridecanol (b. p. 116°/0·6 mm. ; f. p. 29·5° ; 75%), and the latter converted into the bromide, b. p. 114°/0·8 mm. (Reid, Ruhoff, and Burnett, *ibid.*, 1935, **15**, 24). Reaction with malonic ester in the usual manner, followed by hydrolysis and decarboxylation at 180—200° and then distillation, yielded *n*-pentadecanoic acid, b. p. 165—168°/0·8 mm., f. p. 50°.

The acid was then brominated and the product hydrolysed with aqueous sodium hydroxide as described for the corresponding 2-hydroxynonanoic acid (Part III ; *loc. cit.*), to give 2-hydroxypentadecanoic acid (85%), colourless plates (from benzene), m. p. 84° ; *ethyl* 2-*hydroxypentadecanoate* crystallised from light petroleum at −10° in plates, m. p. 48° (Found : C, 70·2; H, 11·9. $C_{16}H_{32}O_3$ requires C, 70·6; H, 11·9%).

Reaction of the foregoing hydroxy-acid with acetyl chloride as usual, gave *2-acetoxypentadecanoic acid*, a sample of which separated from light petroleum at 0° in long needles, m. p. 51—52° (Found : C, 68·4; H, 10·7. $C_{17}H_{32}O_4$ requires C, 68·0; H, 10·7%); the remaining acid was treated with thionyl chloride to give *2-acetoxypentadecanoyl chloride* as a colourless oil, b. p. 166°/0·6 mm. (80%) (Found : Cl, 10·7. $C_{17}H_{31}O_3Cl$ requires Cl, 11·1%).

5-Hydroxy-4-keto-octadecanoic lactone. Reaction of the foregoing acid chloride and tribenzyl sodioethane-1 : 1 : 2-tricarboxylate followed by debenzylation, decarboxylation, hydrolysis with aqueous-ethanolic sulphuric acid, and finally esterification with ethanol according to the general procedures yielded an oil which was fractionally distilled, the material of b. p. 180—205°/0·1—0·5 mm. being collected (8 g., 16%); a large residue remained undistilled. Crystallisation of the distillate from light petroleum at −10° gave a product of m. p. 65—67° (2 g.), a further 4 g. of the same material being obtained similarly from the distillation residue. Combined solids were recrystallised from light petroleum, giving the *keto-lactone* as plates, m. p. 69—69·5° (Found : C, 72·9; H, 10·9. $C_{18}H_{32}O_3$ requires C, 73·0; H, 10·8%).

The mother-liquors from the above crystallisations gave on distillation *ethyl 5-hydroxy-4-keto-octadecanoate* (4 g.) as a pale yellow oil, b. p. 190°/0·5 mm., n_D^{20} 1·4508 (Found : C, 70·7; H, 11·3. $C_{20}H_{38}O_4$ requires C, 70·1; H, 11·2%).

A sample of the latter (0·5 g.) was recovered apparently unchanged after being heated at 120°/0·5 mm. or at 200°/1 atm. for 1 hour, but in the presence of toluene-*p*-sulphonic acid (10 mg.) under the latter conditions the product solidified on cooling and yielded on crystallisation from light petroleum, the above keto-lactone (0·2 g.), m. p. 69° undepressed on admixture with authentic material.

4 : 5-*Dihydroxyoctadecanoic* ***5-lactone.*** Hydrogenation of the foregoing keto-lactone (4 g.) in ethanol over Raney nickel W7 proceeded rapidly and ceased when one mol. of hydrogen had been taken up. The filtered solution was evaporated to dryness under reduced pressure and the residue repeatedly crystallised from light petroleum, to give the *hydroxy-lactone* (1·9 g.) as plates, m. p. 57—58° (Found : C, 72·7; H, 11·1. $C_{18}H_{34}O_3$ requires C, 72·5; H, 11·4%).

Attempts to isolate the other isomer from the filtrates were abandoned after materials of indefinite m. p. were obtained.

4 : 5-*Dihydroxyoctadecanoic* ***4-lactone.*** The mother-liquor obtained after separation of the 5-lactone from the distillation residue was refluxed for 3 hours with ethanol (150 c.c.) and concentrated sulphuric acid (1·5 c.c.). After addition of water, the ester was extracted with ethyl acetate–light petroleum (b. p. 60—80°). The combined organic layers were washed with potassium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. The resulting crude ester was hydrogenated in ethanol, using Raney nickel W7 catalyst, until absorption ceased (1·0 l.). Evaporation of the filtered solution furnished an oil which was refluxed with N-sodium hydroxide (150 c.c.). The acidified solution was extracted with ethyl acetate, the extracts being washed with water and distilled. A pale yellow oil (3·5 g.), b. p. 200—208°/0·5 mm., which partly crystallised when kept, was thus obtained. This material, which presumably contained both isomers of the γ-lactone, was repeatedly recrystallised from light petroleum (b. p. 60—80°), to give slightly impure **4 : 5-***dihydroxy-octadecanoic* ***4-lactone,*** clusters of prisms, m. p. 66—68°, depressed to 45—50° by admixture with the isomeric 5-lactone (Found : C, 71·8; H, 11·3. $C_{18}H_{34}O_3$ requires C, 72·5; H, 11·4%).

II. *Synthesis using the Alkoxy-ketone Route.*—*2-Methoxypentadecanoic acid.* (*a*) *n*-Pentadecanoic acid (80 g.) was brominated with thionyl chloride and bromine (Part III, *loc. cit.*), and the crude bromo-acid chloride treated with methanol and worked up as before. The product was carefully fractionated *in vacuo* through a short Fenske column, fractions of b. p. 151—155°/0·6 mm. having n_D^{20} 1·4606—1·4617 being collected (89%).

The resulting methyl 2-bromopentadecanoate was then added with stirring to a boiling solution of sodium methoxide (from 10 g. of metal) in magnesium-dried methanol (200 ml.), and the mixture was refluxed for 4 hours. Aqueous sodium hydroxide (30 ml. of 10N.) was then added and, after a further 0·5 hour's refluxing, the methanol was removed in steam, and the residue acidified with excess of sulphuric acid, the oily acid being extracted with light petroleum–ethyl acetate (1 : 1). Evaporation of the organic extract furnished almost pure *methoxy-acid,* which was purified by crystallisation from light petroleum (400 ml.) at 0°, whence it separated in colourless plates, m. p. 51—52° (yield, 81—95%) (Found : C, 70·9; H, 11·8. $C_{16}H_{32}O_3$ requires C, 70·6; H, 11·8%).

(*b*) To a suspension of dry sodium ethoxide (from 16·6 g. of metal; 0·72 mol.) in dry ethyl carbonate (700 ml.), methyl methoxyacetate (75 g., 0·72 mol.) was added and the mixture slowly distilled through a short Fenske column until methanol and ethanol ceased to be evolved and the

temperature of the vapours rose to 123°. *n*-Tridecyl iodide (110 g., 0·36 mol.; b. p. 115°/0·7 mm., n_D^{20} 1·4810) was then added to the refluxing slurry of sodiomethoxymalonic ester, in portions with stirring and, after 5 hours' reaction under reflux, the cooled mixture was poured into excess of dilute sulphuric acid. The neutral products were isolated in the usual manner and distilled, material of b. p. 135—175°/0·5—0·7 mm. (mainly 140°) being collected. The resulting ester was hydrolysed and acidic material isolated and decarboxylated as usual. Distillation afforded 2-methoxypentadecanoic acid (60 g.), b. p. 154°/0·2 mm., f. p. 48°, which was purified with negligible loss by crystallisation from light petroleum, as before.

Methyl 4-keto-5-methoxyoctadecanoate. Attempts to isolate 2-methoxypentadecanoyl chloride from the reaction of the acid with thionyl chloride were unsuccessful on account of persistent foaming and slight decomposition during attempted distillation. The chloride was therefore generated *in situ* with oxalyl chloride and used without isolation as follows. 2-Methoxypentadecanoic acid (54 g., 0·2 mol.) was covered with benzene (AnalaR; 200 ml.), and oxalyl chloride (70 g.) added. After the mixture had been kept overnight at room temperature, all solid had dissolved and the mixture was refluxed for 0·5 hour with little evident further reaction. Excess of oxalyl chloride was then removed by distillation through a short Fenske column until the vapour temperature rose to 80°, more benzene being added when necessary. Finally, all the solvent was distilled off under reduced pressure and the residual chloride in fresh benzene (100 ml.) treated with tribenzyl sodioethane-1 : 1 : 2-tricarboxylate in the usual manner. The product was hydrogenated in ethyl methyl ketone (300 ml.) over palladised strontium carbonate (10 g.; 10% Pd) and then decarboxylated, and the residue esterified with methanol by the Soxhlet method (Part IV, *loc. cit.*). Distillation gave, after a fore-run of starting materials, the *ester* as a colourless liquid, b. p. 165—167°/0·3 mm., n_D^{20} 1·4502 (40 g.) (Found: C, 69·7; H, 11·3. $C_{20}H_{38}O_4$ requires C, 70·2; H, 11·1%).

The free *acid* obtained by hydrolysis separated from light petroleum in plates, m. p. 50·5—51·5° (Found: C, 69·2; H, 10·5. $C_{19}H_{36}O_4$ requires C, 69·5; H, 11·0%).

4-Hydroxy-5-methoxyoctadecanoic 4-lactone (VII). The foregoing ester (34 g.) was hydrogenated in ethanolic solution over Raney nickel W7, and the product hydrolysed and distilled, yielding the *lactone* as a colourless oil (30 g.), b. p. 186°/0·5 mm., n_D^{20} 1·4587 (Found: C, 72·8; H, 11·1. $C_{19}H_{36}O_3$ requires C, 73·1; H, 11·5%). When kept, the product, a mixture of the two isomers, solidified and had f. p. 29—22°.

Reaction of (VII) *with hydrogen bromide.* The lactone (VII) (5 g.) was treated with hydrogen bromide–acetic acid–sulphuric acid according to the general procedure. The reaction product (A) partly solidified (Found: Br, 33·2. $C_{18}H_{34}O_2Br_2$ requires Br, 36·2%) and on crystallisation from light petroleum at 0° furnished erythro-4 : 5-*dibromo-octadecanoic acid* as thin rectangular plates, m. p. 64—64·5° (Found: C, 49·0; H, 7·3. $C_{18}H_{34}O_2Br_2$ requires C, 48·9; H, 7·7%).

The filtrate was evaporated and the residue esterified azeotropically with ethanol. Passage of the resulting crude ethyl ester in light petroleum (200 ml.) through a column (12″) of active alumina, followed by elution with the same solvent (400 ml.) and evaporation of the combined eluates, furnished a pale yellow oil, which distilled as a colourless oil (1·7 g.), b. p. 185°/0·3 mm., n_D^{20} 1·4828. Further elution with acetone and benzene did not yield a significant amount of material.

In a later experiment, in which the chromatographic treatment was not carried out, the product was repeatedly fractionally distilled, giving fractions of b. p. 188—198°/0·4 mm., n_D^{20} 1·4795—1·4858, with no obvious separation. The combined fractions, when kept, however, solidified and, on crystallisation from light petroleum (200 ml.) at −20°, furnished a solid of m. p. 32—33° (clear at 35—36°), which on repeated crystallisation from light petroleum at 0° yielded, in an almost pure condition, one of the stereoisomeric *bromo-lactones* (VIII), m. p. 42° (previous sintering at 38°) (Found: C, 59·8; H, 9·3; Br, 21·5. $C_{18}H_{35}O_2Br$ requires C, 59·8; H, 9·1; Br, 22·2%).

cis-*Octadec-4-enoic acid.* A mixture of zinc dust (7 g.), methanol (75 ml.), and hydrogen bromide (1·5 ml. of 10%) was refluxed for 2 minutes in nitrogen, and the crude bromo-acid (A) (7 g.) in methanol (15 ml.) added. The mixture was refluxed for 5 hours, with hourly additions of fresh zinc (1 g.), and the mixture allowed to cool. The flocculent zinc salts were separated from metallic zinc by flotation and finally by extraction with boiling methanol (yield, 4 g.). By repeated crystallisation from methanol, the less soluble zinc salt of the *trans*-acid, m. p. 123—125°, was obtained pure, but attempts to isolate the zinc salt of the *cis*-acid were not completely successful, a material of m. p. 99—103° being eventually obtained.

Decomposition of the latter (150 mg.) by shaking its ethereal suspension with dilute sulphuric acid, followed by evaporation to dryness, furnished a product still containing some *trans*-acid.

Thus, successive cooling of the product in light petroleum solution to room temperature and 0° yielded *trans*-acid (m. p. 58—59° and 56—58°; 12 mg. in all) but at −30° the cis-*acid* was obtained as colourless plates, m. p. 41° (Found: C, 76·6; H, 11·8%; I.V., 89·5. $C_{18}H_{34}O_2$ requires C, 76·6; H, 12·1%; I.V., 89·9). It formed a p-*phenylphenacyl* ester, colourless plates (from acetone), m. p. 65·5—66·5° (Found: C, 80·2; H, 8·8. $C_{32}H_{44}O_3$ requires C, 80·7; H, 9·2%).

An improved procedure consists of decomposing the combined zinc salts, followed by fractional crystallisation of the resulting free acids from light petroleum, as above.

trans-*Octadec-4-enoic acid.* Debromination of solid *erythro*-4 : 5-dibromo-octadecanoic acid (1·9 g.) with zinc in methanol, as previously, furnished a sparingly soluble zinc salt, m. p. 123—125°, decomposed to give the pure trans-*acid* (800 mg.), colourless glistening plates (from light petroleum), m. p. 59·5—60·5° (Found: C, 76·1; H, 12·1%). Determinations of the iodine value (Wijs) gave values of 89·3 (0·5 hour) and 89·8 (3 hours) ($C_{18}H_{34}O_2$ requires I.V., 89·9). It formed a p-*phenylphenacyl* ester, which separated from acetone in lustrous plates, m. p. 89° (Found: C, 80·2; H, 9·1%).

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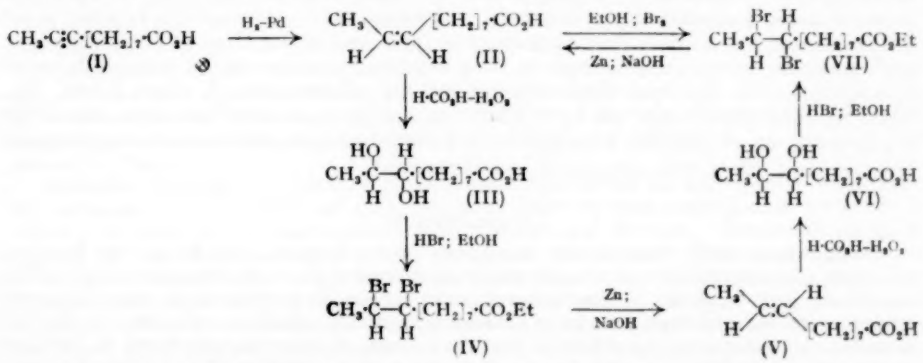
122. *Synthetic Long-chain Aliphatic Compounds. Part VIII.* The Preparation of* cis- *and* trans-*Undec-9-enoic Acids.†*

By D. E. AMES and R. E. BOWMAN.

The acids named in the title have been prepared in a high state of purity *via* the crystalline dihydroxy-acids (III and VI). The *cis*-acid thus obtained differs from that obtained by semi-hydrogenation of the acetylenic acid (I), and this point is discussed.

COLLAUD (*Helv. Chim. Acta*, 1943, **26**, 1064) has described the semi-hydrogenation of undec-9-ynoic acid † (I) and the isolation of *cis*-undec-9-enoic acid (II) by fractional distillation. The required acetylenic acid (I) can be obtained from commercial undecylenic (undec-10-enoic) acid by addition of bromine and reaction of the resulting dibromo-acid with potassium hydroxide at 180° (Krafft, *Ber.*, 1896, **29**, 2234). *trans*-Undec-9-enoic acid (V) has been prepared from the acetylenic acid (I) by addition of hydrogen halide followed by



(I) (II) (VII) (III) (VI) (IV) (V)

[The compounds being optically inactive, (III), (IV), (VI), and (VII) are accompanied by their enantiomorphs. These substances are represented above by the conventional projection formulæ; evidence concerning the spatial positions in αβ-glycols has been summarised by Bader (*J. Amer. Chem. Soc.*, 1948, **70**, 3938).]

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* Part VII, preceding paper. † Geneva nomenclature (CO_2H = 1), throughout.

reduction of the unsaturated halogeno-acid (Krafft and Seldis, *Ber.*, 1900, **33**, 3572; Harris and Smith, *J.*, 1935, 1108) but purification of the product is difficult. We have now prepared the *cis*- and the *trans*-olefinic acid from the corresponding dihydroxy-acids; this procedure is known to furnish products of high purity (Ames and Bowman, *J.*, 1951, 1079, where the stereochemical course of these reactions is discussed).

Undec-9-ynoic acid (I) was hydrogenated until 1·08 mols. of hydrogen had been taken up and the product, isolated by distillation, was found to contain 92% of olefinic acid (II) by determination of the iodine value. Treatment of the crude acid with performic acid (Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786) and hydrolysis of the resulting formoxy-hydroxy-acids furnished *threo*-9 : 10-dihydroxyundecanoic acid (III), readily purified by recrystallisation. This product was heated with hydrogen bromide in acetic–sulphuric acids and the resulting dibromo-acid esterified to give ethyl *erythro*-9 : 10-dibromoundecanoate (IV) which, on debromination and hydrolysis, furnished *trans*-undec-9-enoic acid (V), m. p. 17—18°, I.V. 138·4 (calc., 137·7). Krafft and Seldis (*loc. cit.*) gave m.p. approximately 19° but from their experimental data it seems doubtful if the material was homogeneous; Harris and Smith (*loc. cit.*) used an essentially similar method of preparation but, although the product was purified more rigorously and melted at 20°, it contained some saturated compounds (I.V., 134).

The *trans*-olefinic acid was similarly converted into the crystalline *erythro*-9 : 10-dihydroxyundecanoic acid (VI) and thence into ethyl *threo*-9 : 10-dibromoundecanoate (VII). Debromination and hydrolysis of the latter yielded the pure *cis*-undec-9-enoic acid, m. p. 1—2°, I.V. 138·2. Collaud (*loc. cit.*) gave m. p. 3—3·5° but did not report the iodine value of his material. It is of interest that the crude semihydrogenation product, containing only 92% of olefinic acid, also melted at 1—2°. Thus the presence of significant amounts of saturated acid has only a slight effect on the melting point of the unsaturated acid and this fact illustrates the importance of the iodine value (cf. Smith, *J.*, 1939, 974).

Purification of the crude semihydrogenation product through the dibromo-ester (VII) was also investigated; this was expected to provide the pure *cis*-olefinic acid more conveniently. The crude unsaturated ester in carbon tetrachloride solution was brominated at −10° and the dibromo-ester (VII) separated from saturated contaminants, and from excess of olefinic ester, by fractional distillation. Debromination of (VII) and hydrolysis of the resulting olefinic ester furnished an impure sample of *cis*-undec-9-enoic acid (II), m. p. −3° to −2°, I.V. 138·2. The iodine value indicates that the impurity present is not a saturated compound and is most probably the isomeric *trans*-acid. *trans*-Olefins are known to be formed to some extent during semihydrogenation of acetylenes; *e.g.*, Sondheimer (*J.*, 1950, 879) showed that *cis*-hex-3-enol obtained by semihydrogenation of hex-3-ynol contained a significant proportion of the *trans*-isomer. Although the evidence is not yet conclusive, we consider that on account of these results and those of Sondheimer (*loc. cit.*), particular care should be taken in the purification of olefinic acids obtained by semihydrogenation of acetylenic acids (Strong and his collaborators, *J. Amer. Chem. Soc.*, 1948, **70**, 1699, 3391; 1950, **72**, 2116, 4263); indeed, it is our experience that even in the higher series where both the *trans*-olefinic and the saturated acids are solids their removal requires much effort with consequent loss of material.

Experimental

Undec-9-ynoic Acid.—Commercial undecylenic (undec-10-enoic) acid (60 g.) was dissolved in carbon tetrachloride (200 c.c.) and bromine (42 g.) added gradually, the temperature of the mass being kept below 30°. After removal of the solvent by distillation *in vacuo*, the crude dibromo-acid was added to a solution of potassium hydroxide (135 g.) in water (80 c.c.), and the mixture was heated in an open flask so that the internal temperature rose slowly to 180° and remained there for 30 minutes (cf. Harris and Smith, *loc. cit.*). Water (400 c.c.) was added and the solution acidified, the product being extracted with ethyl acetate. Distillation furnished a colourless oil, b. p. 134—138°/0·7 mm., which rapidly solidified. This procedure consistently yielded 43—47 g. of material, f. p. between 42° and 46°. Crystallisation of it (46 g.) from light petroleum (150 c.c.; b. p. 40—60°) furnished undec-9-ynoic acid (I) (21 g.), m. p. 58—59°. A second crop (7 g.) was obtained at 0° (total yield : 28 g., 47% calc. on the undecylenic acid).

The pure acid, m. p. 61°, was isolated by two further recrystallisations from light petroleum (b. p. 40—60°).

Semihydrogenation of Undec-9-ynoic Acid.—The acid (32 g.) in ethyl acetate (180 c.c.) was hydrogenated in the presence of palladised calcium carbonate (1 g.; 0·5% of Pd) until 4·3 l. (1·08 mols.) had been taken up. Distillation of the filtered solution yielded crude *cis*-undec-9-enoic acid (30 g.) as a colourless oil, b. p. 123—124°/0·8 mm., m. p. 1—2° (capillary) (Found: I.V., 127·1. Calc. for 1 ⁼ in $C_{11}H_{20}O_2$: I.V., 137·7. Thus the material contains 92% of undecenoic acid).

threo-9 : 10-*Dihydroxyundecanoic Acid.*—The foregoing acid (29 g.) was treated with formic acid (90 c.c.) and hydrogen peroxide (20 c.c.; 100-vol.) under the conditions described by Swern *et al.* (*loc. cit.*). The residue, obtained after evaporation of volatile material, was refluxed with excess of sodium hydroxide solution (2N) and poured into dilute sulphuric acid (2N), the product being extracted with warm ethyl acetate. The extracts were washed twice with water, dried (Na_2SO_4), and concentrated to 100 c.c. threo-9 : 10-*Dihydroxyundecanoic acid*, which separated on cooling, recrystallised from ethyl acetate as plates, m. p. 82—83° (9·5 g.) (Found: C, 60·8; H, 9·9. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·2%).

trans-*Undec-9-enoic Acid.*—The foregoing dihydroxy-acid (12·7 g.) was treated with hydrogen bromide in acetic–sulphuric acids, and the product esterified with ethanol by the method previously described (Ames and Bowman, *loc. cit.*). *Ethyl* erythro-9 : 10-*dibromoundecanoate* (19·0 g.) distilled as an almost colourless oil, b. p. 149—152°/0·5 mm., n_D^{20} 1·4926 (Found: C, 41·9; H, 6·5. $C_{13}H_{24}O_2Br_2$ requires C, 42·0; H, 6·5%). Debromination of this product by the standard method (*idem*, *ibid.*) furnished *ethyl* trans-*undec-9-enoate* (9·9 g.) as a colourless oil, b. p. 87—89°/0·5 mm., n_D^{20} 1·4406 (Found: C, 73·6; H, 11·5%; I.V., 118·8. $C_{13}H_{24}O_2$ requires C, 73·5; H, 11·4%; I.V., 119·6).

The olefinic ester (9·8 g.) was hydrolysed by ethanolic potassium hydroxide solution in an atmosphere of nitrogen, and the resulting *trans*-undec-9-enoic acid (7·8 g.) distilled as a colourless oil, b. p. 121—123°/0·7 mm., n_D^{20} 1·4519, m. p. 17—18° (capillary) (Found: I.V., 138·4).

erythro-9 : 10-*Dihydroxyundecanoic Acid.*—The *trans*-olefinic acid (7·5 g.) was converted into the corresponding dihydroxy-acid as in the previous case. erythro-9 : 10-*Dihydroxyundecanoic acid* (4·6 g.) separated from ethyl acetate in large, lustrous plates, m. p. 82—83° (Found: C, 60·5; H, 10·2. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·2%). This product was less soluble in ethyl acetate than the *threo*-isomer, which also melted at 82—83°; a mixture of the two isomers melted at 71—72°. An attempt to prepare the *erythro*-dihydroxy-acid directly from the crude *cis*-undec-9-enoic acid by hydrogen peroxide–osmic acid in acetic acid (Dorée and Pepper, *J.*, 1942, 477) was unsuccessful, giving only a small yield of a heterogeneous product.

cis-*Undec-9-enoic Acid.*—Treatment of the *erythro*-dihydroxy-acid (4·0 g.) with hydrogen bromide in acetic–sulphuric acids and esterification of the product with ethanol in the usual manner furnished *ethyl* threo-9 : 10-*dibromoundecanoate* (5·6 g.) as a pale yellow oil, b. p. 149—152°/0·6 mm., n_D^{20} 1·4937 (Found: C, 42·1; H, 6·8. $C_{13}H_{24}O_2Br_2$ requires C, 42·0; H, 6·5%). The latter was debrominated by the general procedure to give *ethyl* cis-*undec-9-enoate* (2·6 g.), a colourless oil, b. p. 88—90°/0·6 mm., n_D^{20} 1·4418 (Found: C, 74·0; H, 11·9%; I.V., 118·4. $C_{13}H_{24}O_2$ requires C, 73·5; H, 11·4%; I.V., 119·6). Hydrolysis of this ester, as in the previous case, afforded pure *cis*-undec-9-enoic acid (1·8 g.) as a colourless oil, b.p. 118—120°/0·8 mm., n_D^{20} 1·4530, m. p. 1—2° (capillary) (Found: I.V., 138·2). The *p*-phenylphenacyl ester crystallised from ethanol in plates, m. p. 64·5—65°, unchanged by recrystallisation. Collaud (*loc. cit.*) gave m. p. 65—66°.

Attempted Purification of Crude cis-*Undec-9-enoic Acid through the Dibromide.*—A sample of the crude acid (3·8 g.) obtained by semihydrogenation was esterified azeotropically with ethanol (60 c.c.), benzene (60 c.c.), and concentrated sulphuric acid (0·5 c.c.). Isolated in the usual manner, the ester was dissolved in carbon tetrachloride (50 c.c.), and the solution was cooled to −10° while bromine (2·5 g.; 80% of the amount calculated for the undecenoic acid present) in carbon tetrachloride (50 c.c.) was added in small portions with shaking. The mixture was allowed to warm to room temperature, washed with potassium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was repeatedly fractionated under reduced pressure until no further purification could be effected, as shown by *n*. Ethyl *threo*-9 : 10-dibromoundecanoate, b. p. 147—148°/0·5 mm., was thus obtained as a colourless oil, n_D^{20} 1·4925. Debromination of this material (17 g.) by the general procedure yielded ethyl *cis*-undec-9-enoate which distilled as a colourless oil, b. p. 92—94°/0·4 mm., n_D^{20} 1·4417 (8·5 g.) (Found: I.V., 119·6. Calc. for $C_{13}H_{24}O_2$: I.V., 119·6). The *cis*-undec-9-enoic acid (7 g.) obtained by hydrolysis was slightly impure (b. p. 117—119°/0·5 mm., n_D^{20} 1·4530, m. p. −3°

to −2° in a capillary tube) (Found: C, 71·9; H, 11·0%; I.V., 137·6. Calc. for $C_{11}H_{20}O_2$: C, 71·7; H, 10·9%; I.V., 137·7). The *p*-phenylphenacyl ester prepared from this product was also slightly impure (m. p. 61°), but could not be purified further by recrystallisation (Found: C, 79·1; H, 8·1. Calc. for $C_{25}H_{30}O_3$: C, 79·3; H, 8·0%).

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123. *New Intermediates and Dyes. Part II.* Preparation and Properties of* 4-tert.-*Butylphthalic Anhydride. Orientation of its Condensation Products with Benzenoid Hydrocarbons.*

By BRIAN W. LARNER and ARNOLD T. PETERS.

The properties of 4-*tert.*-butylphthalic anhydride are examined and many new derivatives are prepared. The carbonyl group *para* to the *tert.*-butyl group is the more reactive in Friedel–Crafts condensations with benzenoid hydrocarbons. The orientation of the derived *tert.*-butylbenzoylbenzoic acids was shown by decarboxylation to the respective *tert.*-butylbenzophenones, which were compared with synthetic specimens.

4-*tert.*-BUTYL-*o*-XYLENE was prepared in 73% yield by interaction of a slight excess of *tert.*-butyl chloride and *o*-xylene in presence of anhydrous ferric chloride at room temperature, whereby loss of *tert.*-butyl chloride (at 70—80°) was eliminated and no di-*tert.*-butyl-*o*-xylene was formed (cf. Nightingale and Janes, *J. Amer. Chem. Soc.*, 1944, **66**, 154; Contractor and Peters, *J.*, 1949, 1314). 4-*tert.*-Butyl-*o*-xylene was unchanged by chromic acid in boiling acetic acid, but was oxidised with potassium permanganate in boiling aqueous pyridine to give 50% of 4-*tert.*-butylphthalic acid and 9% of 4-*tert.*-butyl-2-methylbenzoic acid, which are converted by boiling acetic anhydride into the respective anhydrides. The resistance of the *tert.*-butyl group to oxidation, thus illustrated, has already been discussed (Contractor and Peters, *loc. cit.*).

The constitution of 4-*tert.*-butylphthalic anhydride (I) was confirmed by its conversion into trimellitic acid by dilute nitric acid at 200—210°.

No derivative of this anhydride (I) has been described in the literature, and we have now examined its reactions and compared the effect of the *tert.*-butyl group with that of other alkyl groups in reactions of alkylphthalic anhydrides.

With aqueous ammonia in boiling alcohol, the anhydride gave diammonium 4-*tert.*-butylphthalate, whilst with solely aqueous ammonia at 330° 4-*tert.*-butylphthalimide was formed; the *N*-methylphthalimide was prepared similarly. The anhydride was further characterised as the phthalanil and phthalanildianisidide, and as the pyridinium *tert.*-butylphthalanil of sulphanilic acid and metanilic acid, respectively. It can thus be used as a reagent for the identification of amines, and also of aromatic sulphonic acids (at least, of the two mentioned) (cf. Cross and Chen, *J. Soc. Dyers and Col.*, 1943, **59**, 144). The anhydride was also converted into the liquid dimethyl and diethyl, and the solid di-(*p*-nitrobenzyl) 4-*tert.*-butylphthalate.

Condensation of a 4-alkylphthalic anhydride with an alkylbenzene could theoretically produce six isomeric dialkylbenzoylbenzoic acids; the fact that *meta*-condensation has not been observed reduces this number probably to four; and it has been shown that reaction occurs mainly at the *p*-position of the alkylbenzene. Thus, Peters and Rowe (*J.*, 1945, 181) condensed phthalic anhydride with *tert.*-butylbenzene to give *o*-*p*'-*tert.*-butylbenzoylbenzoic acid, and Fieser and Price (*J. Amer. Chem. Soc.*, 1936, **58**, 1840) obtained β-*p*-*tert.*-butylbenzoylpropionic acid from succinic anhydride.

The 4-*tert.*-butyl anhydride was condensed with benzene, toluene, and *tert.*-butyl-

* Part I, *J.*, 1949, 1314.

benzene severally in the Friedel–Crafts reaction, using aluminium chloride. Benzene afforded mainly 2-benzoyl-5-*tert.*-butylbenzoic acid; Hayashi (*J.*, 1927, 2516; 1930, 1513) obtained mixed acids in a similar reaction using 4-methylphthalic anhydride. In the case of toluene, the carboxylic acids derived from the *tert.*-butyl anhydride were fractionally crystallised, yielding mainly 5-*tert.*-butyl-2-*p*-toluoylbenzoic acid; on dissolution in cold concentrated sulphuric acid, the latter isomerised to a mixture of *tert.*-butyltoluoylbenzoic acids, a similar phenomenon being observed by Hayashi (*loc. cit.*) in the case of the chlorohydroxymethylbenzoylbenzoic acids derived from *p*-chlorophenol and 3- or 4-methylphthalic acid. *tert.*-Butylbenzene afforded almost exclusively 5-*tert.*-butyl-2-*p*-*tert.*-butylbenzoylbenzoic acid, which was readily purified and was unchanged after treatment with sulphuric acid at room temperature for 24 hours.

For orientation the *tert.*-butylbenzoylbenzoic acids were decarboxylated by copper bronze; the catalyst is probably a trace of the copper salt of the carboxylic acid; cessation of evolution of carbon dioxide is accompanied by precipitation of a trace of fine black powder (cf. Newmann and Lord, *J. Amer. Chem. Soc.*, 1944, **66**, 733, who used a trace of the copper salt as catalyst in the decarboxylation of carboxylic acids). The resulting alkylbenzophenones were characterised by comparison with synthetic specimens, except in the case of benzene, the mixed acids from which did not give a pure benzophenone. The preparation of relevant intermediates is now described.

p-*tert.*-Butyltoluene could not be oxidsed by Bialobrzeski's chromic–acetic acid method (*Ber.*, 1897, **30**, 1773). Oxidation by permanganate in aqueous pyridine (see Experimental) gave a 35% yield of *p*-*tert.*-butylbenzoic acid.

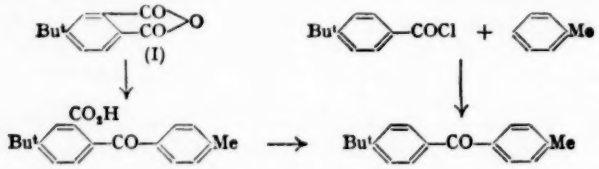
Reaction of *tert.*-butyl chloride with excess of toluene in presence of aluminium chloride (cf. Baur, *Ber.*, 1891, **24**, 2833), to give mainly *m*-*tert.*-butyltoluene, was very sensitive to temperature conditions; in one experiment, where we used excess of aluminium chloride at 25°, a dimethylanthracene was obtained, probably identical with that described by Anschütz (*Annalen*, 1886, **235**, 152; cf. Anschütz and Immendorff, *Ber.*, 1884, **17**, 2816; Zincke and Wackendoerff, *Ber.*, 1877, **10**, 1481; Lavaux, *Ann. Chim.*, 1910, **20**, 468). Buu-Hoï and Cagniant (*Bull. Soc. chim.*, 1942, **9**, 887) also report that this reaction gives mainly the *m*-isomer, and state that the results of Shoesmith and McGechen (*J.*, 1930, 2231) are probably due to the fact that both *m*- and *p*-*tert.*-butyltoluene are converted by concentrated sulphuric acid into mixed isomers. Serijan *et al.* (*J. Amer. Chem. Soc.*, 1949, **71**, 873) agree and add that considerable fractionation is necessary (100 plates) to effect separation of the pure *m*-isomer. We found that our impure *m*-*tert.*-butyltoluene, although resistant to chromic acid, was oxidised by permanganate in aqueous pyridine to give good yields of *tert.*-butylbenzoic acid, separable into a little of the *p*-isomer and a product, m. p. 98°, mainly the *m*-isomer, which could not be further purified. Kelbe and Pfeiffer (*Ber.*, 1886, **19**, 1723) used dilute nitric acid as oxidant, but record no details; the m. p. of *m*-*tert.*-butylbenzoic acid is given as 127°.

The liquid 4-*tert.*-butylbenzophenone was prepared (*a*) by condensing *p*-*tert.*-butylbenzoyl chloride with benzene in presence of aluminium chloride, (*b*) from benzoyl chloride and *tert.*-butylbenzene, and (*c*) by decarboxylation of 2-*p*-*tert.*-butylbenzoylbenzoic acid (Peters and Rowe, *J.*, 1945, 181); in each case, the ketone gave mixed oximes, from which a pure oxime, m. p. 150—152°, was readily obtained.

4-*tert.*-Butyl-4′-methylbenzophenone was synthesised from *p*-*tert.*-butylbenzoyl chloride, toluene, and aluminium chloride; the derived pure oxime, m. p. 177·5—178·5°, was converted by rearrangement (method: Beckmann and Barton, *J. Org. Chem.*, 1939, **3**, 300) into 4′-*tert.*-butyl-*p*-toluanilide, identical with a specimen prepared from *p*-*tert.*-butylaniline and *p*-toluoyl chloride. That 5-*tert.*-butyl-2-*p*-toluoylbenzoic acid was the main condensation product of 4-*tert.*-butylphthalic anhydride and toluene was shown by decarboxylation to 4-*tert.*-butyl-4′-methylbenzophenone, the derived oxime being identical with a synthetic sample. Cyclisation of the acid by 20% fuming sulphuric acid was accompanied by isomerisation and gave 2-*tert.*-butyl-7- and -6-methylanthraquinone.

The orientation of 5-*tert.*-butyl-2-*p*-*tert.*-butylbenzoylbenzoic acid, derived from the anhydride (I), was shown by decarboxylation to 4 : 4′-di-*tert.*-butylbenzophenone, m. p. 133—134° (pure oxime, m. p. 195—196°), identical with specimens synthesised from

p-tert.-butylbenzoyl chloride, *tert.*-butylbenzene, and aluminium chloride, or from *tert.*-butylbenzene, carbon tetrachloride, and aluminium chloride (cf. Gomberg and Todd, *J. Amer. Chem. Soc.*, 1917, **39**, 2392, who prepared 4 : 4′-dimethylbenzophenone in an analogous manner). Beckmann rearrangement of the oxime afforded 4 : 4′-di-*tert.*-butylbenzanilide, identical with that synthesised from *p-tert.*-butylbenzoyl chloride and *p-tert.*-butylaniline.



Both *m*- and *p*-bromo-*tert.*-butylbenzene were synthesised, but attempted conversion through the corresponding Grignard reagent and *p-tert.*-butylbenzoyl chloride into 3 : 4′- and 4 : 4′-di-*tert.*-butylbenzophenone, respectively, gave oily mixtures.

Cyclisation of 5-*tert.*-butyl-2-*p-tert.*-butylbenzoylbenzoic acid afforded 2 : 7-di-*tert.*-butylanthraquinone.

Experimental

M. p.s are corrected. Micro-analyses were carried out by Drs. Weiler and Strauss, of Oxford.

4-tert.-*Butyl-o-xylene.*—Anhydrous ferric chloride (1 g.) was added during 30 minutes to a well-stirred mixture of *o*-xylene (106 g., 1 mol.) and *tert.*-butyl chloride (92·5 g., 1 mol.) at room temperature. After the vigorous evolution of hydrogen chloride had subsided, more *tert.*-butyl chloride (20 g.) was added and the mixture stirred for 1 hour and then heated on the water-bath for 15 minutes and filtered (charcoal). 4-*tert.*-Butyl-*o*-xylene, a colourless oil, n^{9} 1·5002, distilled at 211—212° (111 g., 73%) (Found : C, 88·4; H, 11·4. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%).

4-tert.-*Butylphthalic Acid and Anhydride.*—The preparation was much improved as follows : Potassium permanganate (360 g., 2·25 mols.) was added during 1·5 hours to a well-stirred boiling solution of 4-*tert.*-butyl-*o*-xylene (81 g.; 0·5 mol.) in pyridine (500 c.c.) and water (1 l.). The mixture continued to boil without further heating, and, after final refluxing for 30 minutes, excess of permanganate was removed with alcohol, the mixture filtered, and the residue washed well with hot water. Filtrate and washings were distilled to remove pyridine and excess of *tert.*-butyl-*o*-xylene, and concentrated to 300 c.c.; careful addition of hydrochloric acid precipitated a basic potassium salt of 4-*tert.*-butylphthalic acid, which was collected and stirred with hydrochloric acid to yield potassium chloride and impure *tert.*-butylphthalic acid; the latter crystallised from benzene–ligroin (b. p. 60—80°, here and below) in stout, colourless prisms, m. p. 159—161° (59·3 g., 50%) (Found : C, 64·7; H, 6·0. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%). The mixture (100 g.) of potassium chloride and *tert.*-butylphthalic acid was heated with acetic anhydride (200 c.c.), and the orange solution filtered from inorganic salt and distilled, to give 4-*tert.*-butylphthalic anhydride (I), b. p. 311—312°/750 mm., 136°/2 mm., which crystallised from ligroin in colourless plates, m. p. 77° (Found : C, 70·2; H, 5·9. Calc. for $C_{12}H_{12}O_3$: C, 70·6; H, 5·9%). Continuation of the above distillation at 2 mm. gave a pale yellow oil (8·5 g.), b. p. 203—205°/2 mm., which was 4-tert.-*butyl-2-methylbenzoic anhydride* (Found : C, 79·0; H, 8·0. $C_{24}H_{30}O_3$ requires C, 78·7; H, 8·2%). This anhydride was dissolved in boiling dilute sodium hydroxide, and the mixture cooled and acidified; crystallisation of the precipitate from alcohol gave colourless plates, m. p. 142—143°, of 4-*tert.*-butyl-2-methylbenzoic acid, which was readily converted into (I) by further oxidation as above.

Trimellitic Acid.—4-*tert.*-Butylphthalic anhydride (1 g.), nitric acid (*d* 1·42) (4 c.c.), and water (2 c.c.) were heated at 200—210° for 8 hours, to give colourless prisms (from acetic acid), m. p. 228—230°, of trimellitic acid (Found : C, 50·9; H, 2·7. Calc. for $C_9H_6O_6$: C, 51·4; H, 2·9%). Sublimation at 180°/0·8 mm. afforded trimellitic anhydride, m. p. 160°. If nitric acid–water (1 : 2) was used, the anhydride (I) was mainly recovered.

Derivatives of 4-tert.-*Butylphthalic Anhydride* (I).—When the anhydride (2 g.) was refluxed with alcohol (5 c.c.) and aqueous ammonia (*d* 0·88; 5 c.c.) for 2 hours, colourless prisms of *diammonium* 4-tert.-*butylphthalate* (2 g.), m. p. 164° (decomp.), separated (Found : N, 10·4. $C_{12}H_{20}O_4N_2$ requires N, 10·9%). Heating the anhydride (1 g.) and aqueous ammonia (*d* 0·88; 5 c.c.) at 330° and then cooling, gave a clear liquid which solidified and crystallised from alcohol

in colourless prisms, m. p. 133—134°, of 4-tert.-*butylphthalimide* (0·9 g., 90%) (Found : C, 70·7; H, 6·2; N, 6·7. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). It was also formed by heating the above diammonium salt above its m. p.

A solution of the anhydride (1 g.) in 33% aqueous methylamine (10 c.c.) was refluxed for 1 hour and evaporated to a clear liquid, b. p. 314°; on cooling, the solidified product was recrystallised from alcohol in colourless prismatic needles, m. p. 94—94·5°, of 4-tert.-*butyl*-N-*methylphthalimide* (0·8 g., 74%) (Found : C, 72·2; H, 6·9; N, 6·3. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9; N, 6·45%).

Aniline (2 g.) and the anhydride (2 g.) were heated at 180° for 10 minutes, the mixture was extracted with dilute hydrochloric acid, and the 4-tert.-*butylphthalanil* (2·4 g., 90%) crystallised from alcohol in colourless needles, m. p. 185° (Found : C, 77·8; H, 6·1; N, 5·1. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

Sulphanilic acid (2 g.), pyridine (4 c.c.), and the anhydride (I) (2·8 g.) (method : Cross and Chen, *loc. cit.*) were warmed to a clear brown solution, which suddenly became solid. *Pyridinium* 4-tert.-*butylphthalanil*-4′-*sulphonate* (5·1 g., 85%) crystallised from alcohol in colourless prisms, m. p. 228—229° (Found : C, 62·7; H, 5·1; N, 6·5; S, 7·4. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·0; N, 6·4; S, 7·3%). The more soluble 3′-*sulphonate* analogue (4·3 g., 72%) crystallised from aqueous alcohol in colourless prisms, m. p. 213—214° (Found : C, 62·6; H, 5·3; N, 6·2; S, 7·1%).

Di-(4-tert.-*butylphthalanil*)*dianisidide*, prepared by heating dianisidine (1·2 g.) with the anhydride (I) (2 g.) until the whole was solid at 300°, separated from aqueous acetic acid as a brown amorphous solid, m. p. above 330° (Found : N, 4·3. $C_{38}H_{36}O_6N_2$ requires N, 4·5%), unsuitable for identification of dianisidine. Dry hydrogen chloride was introduced into a cooled solution of the anhydride (2·5 g.) in methyl alcohol (20 c.c.) until it was saturated at room temperature. Next morning, alcohol and hydrogen chloride were removed and the oily residue was shaken with aqueous ammonia. *Dimethyl* 4-tert.-*butylphthalate* (2·1 g., 67%) distilled at 169—171°/9·3 mm. as a colourless oil (Found : C, 66·9; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). The diethyl ester (66% yield) distilled at 183°/8 mm.

Di-p-*nitrobenzyl* 4-tert.-*butylphthalate* (method : Reid and Lyman, *J. Amer. Chem. Soc.*, 1917, **39**, 124, 701) separated from 95% alcohol in colourless needles, m. p. 122—113° (Found : C, 63·3; H, 4·7; N, 5·2. $C_{26}H_{24}O_8N_2$ requires C, 63·4; H, 4·9; N, 5·7%).

p-tert.-*Butyltoluene*.—Dry toluene (92 g., 1 mol.), *tert.*-butyl chloride (92·5 g., 1 mol.), and anhydrous ferric chloride (1 g.) gave *p-tert.*-butyltoluene, b. p. 191° (124 g., 88%) (Found : C, 89·2; H, 10·6. Calc. for $C_{11}H_{16}$: C, 89·2; H, 10·8%).

p-tert.-*Butylbenzoic Acid*.—Potassium permanganate (110 g.) was added during 1 hour to a boiling mixture of *p-tert.*-butyltoluene (50 g.) in pyridine (300 c.c.) and water (600 c.c.); if more pyridine is used to obtain complete solution, reaction is violent, whereas complete omission of pyridine led to a poor yield. After a further hour's stirring and removal of manganese dioxide, acidification gave *p-tert.*-butylbenzoic acid (21 g., 35%), which crystallised from ligroin in colourless prismatic needles, m. p. 162—164° (Found : C, 73·7; H, 7·8. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%). The acid (25 g.) was converted by thionyl chloride (25 c.c.) into the chloride (20·5 g., 75%), b. p. 266—273° (Found : C, 67·2; H, 6·7; Cl, 18·1. Calc. for $C_{11}H_{13}OCl$: C, 67·2; H, 6·6; Cl, 18·1%), and thence into the amide, colourless plates (from alcohol), m. p. 173° (Kelbe and Pfeiffer, *Ber.*, 1886, **19**, 1725, give m. p. 171°) (Found : C, 74·4; H, 8·4; N, 7·4. Calc. for $C_{11}H_{15}ON$: C, 74·6; H, 8·5; N, 7·9%).

m-tert.-*Butyltoluene*.—Anhydrous aluminium chloride (10 g.), toluene (125 c.c., 1·2 mols.), and *tert.*-butyl chloride (25 c.c., 0·23 mol.) at 0—5° (temperature important) for 3 hours gave impure *m-tert.*-butyltoluene (13 c.c.), b. p. 186—195° (Found : C, 88·7; H, 10·8. Calc. for $C_{11}H_{16}$: C, 89·2; H, 10·8%). When 20 g. of aluminium chloride were used at 25°, pale yellow plates (from benzene) (2·2 g.), m. p. 225°, with a strong blue fluorescence, were obtained [Found : C, 93·1; H, 6·6%; *M* (in camphor), 200, 202. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%; *M*, 206]. This was almost certainly the dimethylanthracene, m. p. 225°, recorded by Lavaux (*loc. cit.*).

m-tert.-*Butylbenzoic Acid*.—*m-tert.*-Butyltoluene was unchanged by sodium dichromate in boiling acetic acid, or boiling nitric acid of varying strengths, but in pyridine (225 c.c.) and water (150 c.c.), the hydrocarbon (15 g., 0·1 mol.) was oxidised by potassium permanganate (45 g., 0·3 mol.) (at the b. p. for 1 hour) to give a little *p-tert.*-butylbenzoic acid and the more soluble *m*-isomer (11·3 g., 64%), which on crystallisation from ligroin gave colourless prisms, m. p. 98°, unchanged by further recrystallisation from ligroin or acetic acid (Found : C, 73·7; H, 7·8. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%). It probably retains a little of the *p*-isomeride. The derived acid chloride, b. p. 256—260°, afforded an amide, which crystallised from aqueous

alcohol in colourless, prismatic needles, m. p. 107°, unchanged in m. p. on repeated crystallisation (Found : C, 74·1; H, 8·6; N, 7·8. Calc. for $C_{11}H_{15}ON$: C, 74·6; H, 8·5; N, 7·9%).

p-tert.-*Butylaniline*.—To *tert*.-butylbenzene (78 g.) (method of preparation : Bromby *et al.*, *loc. cit.*), nitric acid (*d* 1·5; 78 g.) was added at 20—25° during 3 hours, and the product distilled with steam; unchanged *tert*.-butylbenzene distilled first, followed by the less-volatile *p*-nitro-*tert*.-butylbenzene (63 g., 69%), b. p. 264—268°; this was reduced by Shoesmith and Mackie's method (*J.*, 1928, 2334) to *p-tert*.-butylaniline (41·3 g., 60%), b. p. 248—250°, isolated through the *hydrochloride*, m. p. 270—274° (sealed tube) (Found : C, 64·8; H, 8·7; N, 7·5; Cl, 18·7. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·4; Cl, 19·1%). The acetyl derivative crystallised from aqueous alcohol in plates, m. p. 173°.

m-*Bromo*-tert.-*butylbenzene* (cf. Marvel *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 914, who record no details).—Bromine (24 g., 0·3 mol.) was added slowly to *p-tert*.-butylacetanilide (19 g., 0·1 mol.), acetic acid (75 c.c.), and iron filings (0·1 g.) at 35°. After 5 hours' stirring, the mixture was added to ice-water, and the 2-bromo-4-*tert*.-butylacetanilide crystallised from alcohol in colourless plates, m. p. 156—158° (25 g., 92%) (Found : N, 5·4. Calc. for $C_{12}H_{16}ONBr$: N, 5·2%) (cf. Gelzer, *Ber.*, 1888, **21**, 2941); 11·6 g. were hydrolysed by boiling with hydrochloric acid (20 c.c.) and 95% alcohol (30 c.c.) for 3 hours; concentration gave 2-*bromo*-4-tert.-*butylaniline hydrochloride* (10 g., 88·5%) in colourless plates, m. p. 193—194° (Found : N, 5·4. $C_{10}H_{15}NClBr$ requires N, 5·3%), and thence the free amine, a colourless oil, b. p. 98—99°/0·7 mm. (Found : N, 6·2; Br, 34·3. Calc. for $C_{10}H_{14}NBr$: N, 6·1; Br, 35·1%). The hydrochloride (27 g.) in acetic acid (150 c.c.), water (100 c.c.), and concentrated hydrochloric acid (35 c.c.) at 0°, were treated with sodium nitrite (7·6 g.) in water (50 c.c.), and then added to hypophosphorous acid (180 c.c.). After 3 days, the separated oily *m*-bromo-*tert*.-butylbenzene was extracted and distilled, as a colourless oil, b. p. 222—223°/758 mm. (14 g., 66%), which did not solidify at −15°.

p-*Bromo*-tert.-*butylbenzene*.—The following method is much better than that given by Marvel *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 2773), who employed sunlight and no halogen carrier. Bromine (80 g., 1 mol.) was added slowly to *tert*.-butylbenzene (67 g., 0·5 mol.) and iron filings (1 g.) at room temperature; next morning, addition to water gave an oil, which was washed successively with aqueous sodium hydrogen sulphite, sodium carbonate, and water. *p*-Bromo-*tert*.-butylbenzene distilled as a colourless oil, b. p. 228—229°, f. p. 10—11° (77·3 g., 73%).

p-tert.-*Butylbenzophenone*.—(*a*) (cf. Bergmann *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2748) *p-tert*.-Butylbenzoyl chloride (4·9 g.) in dry benzene (25 c.c.) was treated with aluminium chloride (10 g.) at 20°. After the mixture had been kept overnight and then decomposed, *p-tert*.-butylbenzophenone (3·9 g., 66%), b. p. 151—160°, was obtained which gave an oxime (2·2 g., 87%), mixed isomers, m. p. 125—141°, and thence by crystallisation from alcohol, a pure *oxime*, colourless prismatic needles, m. p. 150—152° (Found : N, 5·2. $C_{17}H_{19}ON$ requires N, 5·5%). The general method used in preparing oximes described in this paper was to add hydroxylamine hydrochloride (1·4 g., 0·02 mol.) in water (3 c.c.) to the ketone (0·01 mol.) in alcohol (15 c.c.), followed by potassium hydroxide (2·25 g., 0·04 mol.) in water (2·5 c.c.), the mixture being refluxed for 5 hours and then added to water (60 c.c.).

(*b*) Benzoyl chloride (4·2 g.) and *tert*.-butylbenzene (25 c.c.) in presence of aluminium chloride (10 g.) similarly gave *p-tert*.-butylbenzophenone (4·5 g., 76%) and thence the impure, m. p. 125—140°, and pure oxime, m. p. 150—152°, identical with that prepared by method (*a*).

(*c*) *o-p'-tert*.-Butylbenzoylbenzoic acid (5 g.) was decarboxylated by heating it with a little copper bronze at 250° until evolution of carbon dioxide ceased. After the mixture had cooled, alcohol was added and the whole filtered from a trace of black powder; the alcohol was removed and the residue distilled, to yield *p-tert*.-butylbenzophenone (3·1 g., 73%), b. p. 130—140°/0·5 mm., and thence the pure oxime, m. p. and mixed m. p. with those prepared by methods (*a*) and (*b*), 150—152°.

Condensation of 4-tert.-*Butylphthalic Anhydride* (I) *with Toluene ;* 4- *and* 5-tert.-*Butyl*-2-p-*toluoylbenzoic Acid*.—The anhydride (I) (10 g., 0·05 mol.), aluminium chloride (13·3 g., 0·1 mol.), and excess of dry toluene (50 c.c.) were stirred on the steam-bath for 3 hours; after decomposition, toluene was removed with steam, and the residue extracted with boiling 5% aqueous sodium carbonate; acidification of the alkaline extract gave a colourless precipitate, m. p. 100—120° (13·4 g., 90%), of mixed carboxylic acids. Crystallisation from benzene–ligroin and then from acetic acid afforded 5-tert.-*butyl*-2-p-*toluoylbenzoic acid* (*A*), colourless prisms (1·5 g.), m. p. 204—205° (Found : C, 77·3; H, 6·7. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%). The mother-liquors yielded an impure isomer (*B*) (1 g.), m. p. 165—175°, depressed in m. p. on admixture with (*A*). On leaving either (*A*) or (*B*) in concentrated sulphuric acid at room temperature for 24 hours, isomerisation occurred to give a similar mixture of acids, m. p.

130—140°. The carboxylic acid (*A*) (1 g.) was heated with 20% fuming sulphuric acid (5 c.c.) at 95° for 3 hours and the resulting deep red solution poured on ice. The solid was extracted with dilute aqueous ammonia, and the residue crystallised from methyl alcohol in lemon-yellow prisms, m. p. 83—95°, not purified further by crystallisation or chromatographic means (Found: C, 81·7; H, 6·3. Calc. for $C_{19}H_{18}O_2$: C, 82·0; H, 6·5%). This was probably a mixture of 2-*tert.*-butyl-7- and -6-methylanthraquinone.

4-tert.-*Butyl*-4′-*methylbenzophenone*.—Aluminium chloride (20 g., 0·15 mol.) was added to *p-tert.*-butylbenzoyl chloride (9·8 g., 0·05 mol.), dry toluene (9·2 g., 0·1 mol.), and carbon disulphide (15 c.c.) at room temperature, and the whole refluxed for 3 hours. By the usual procedure, 4-tert.-*butyl*-4′-*methylbenzophenone* distilled as a very pale blue oil (7·4 g., 59%), b. p. 148—150°/0·4 mm. (Found: C, 85·7; H, 7·9. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%). The *p*-nitrophenylhydrazone could not be prepared, but the derived *oxime*, m. p. 153—163°, was crystallised several times to yield a pure isomer, colourless prismatic needles (from aqueous alcohol), m. p. 177·5—178·5° (Found: C, 80·8; H, 8·0; N, 5·4. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9; N, 5·2%). Rearrangement (method: Beckmann and Barton, *J. Org. Chem.*, 1939, **3**, 300) of the pure oxime (0·5 g.) with phosphorus pentachloride (1 g.) in benzene (15 c.c.) gave 4′-*tert.*-butyl-*p*-toluanilide (0·4 g.), which crystallised from benzene–ligroin in colourless prisms, m. p. and mixed m. p. 150—151° (see below).

4-tert.-*Butylbenzo*-p-*toluidide*.—*p-tert.*-Butylbenzoyl chloride (from 1·7 g. of acid) was treated with a solution of *p*-toluidine (1·1 g.) in benzene (10 c.c.); reaction was vigorous and after 30 minutes' refluxing, filtration, and concentration, the *toluidide* was obtained as colourless prisms (benzene–ligroin), m. p. 129—130° (1·6 g.) (Found: N, 4·8. $C_{18}H_{21}ON$ requires N, 5·2%).

4′-tert.-*Butyl*-p-*toluanilide*.—*p*-Toluic acid (2·7 g.) was converted into the chloride with thionyl chloride; refluxing with *p-tert.*-butylaniline (3 g.) in benzene (20 c.c.) for 2 hours gave colourless silky needles, m. p. 150—151°, of the *toluanilide* (1·8 g.) (Found: N, 5·2. $C_{18}H_{21}ON$ requires N, 5·2%), identical with that obtained by the above rearrangement.

Decarboxylation of 5-tert.-*Butyl*-2-p-*toluoylbenzoic Acid*.—The acid (1 g.) was heated with a little copper bronze at 250° until reaction ceased; alcohol was added and the mixture filtered; to the filtrate, hydroxylamine hydrochloride (0·4 g.) and potassium hydroxide (0·75 g.) were added and 4-*tert.*-butyl-4′-methylbenzophenone oxime, m. p. and mixed m. p. with the above specimen, 177·5—178·5°, was obtained.

m-tert.-Butylbenzoyl chloride, toluene, and aluminium chloride afforded a pale blue oil, b. p. 172—174°/2·2 mm., which gave a trace of 4-*tert.*-butyl-4′-methylbenzophenone oxime, but no further solid product.

Condensation of 4-tert.-*Butylphthalic Anhydride* (I) *with* tert.-*Butylbenzene;* 5-tert.-*Butyl*-2-p-tert.-*butylbenzoylbenzoic Acid*.—The anhydride (I) (10 g., 0·05 mol.), excess of *tert.*-butylbenzene (50 c.c.), and aluminium chloride (13·3 g., 0·1 mol.) on the boiling water-bath gave, by the usual procedure, the *carboxylic acid* (10·1 g., 60%), which crystallised from aqueous acetic acid and then benzene–ligroin in colourless prisms, m. p. 234—235° (Found: C, 77·6; H, 7·6. $C_{22}H_{26}O_3$ requires C, 78·1; H, 7·7%). There was no isomerisation when the acid was kept in concentrated sulphuric acid for 24 hours at room temperature. No isomer could be detected in the mother-liquors from the above crystallisations, but some 4-*tert.*-butylphthalic acid, m. p. and mixed m. p. 152°, was isolated.

2 : 7-*Di*-tert.-*butylanthraquinone*.—Cyclisation of 5-*tert.*-butyl-2-*p-tert.*-butylbenzoylbenzoic acid (1 g.) by 20% fuming sulphuric acid (5 c.c.) at 95° for 4 hours gave, after addition to water and extraction of the precipitate with aqueous ammonia, 2 : 7-*di*-tert.-*butylanthraquinone* (0·6 g.), which crystallised from methyl alcohol in pale yellow prisms, m. p. 119—121° (Found: C, 82·3; H, 7·6. $C_{22}H_{24}O_2$ requires C, 82·5; H, 7·5%). An attempt by Elbs and Wittick's method (*Ber.*, 1885, **18**, 348) to prepare a dimethylanthracene from toluene and chloroform gave only a resin.

4 : 4′-*Di*-tert.-*butylbenzophenone*.—(*a*) p-*tert.*-Butylbenzoyl chloride (7·5 g.) was added slowly to dry *tert.*-butylbenzene (13 g.) and aluminium chloride (10 g.) at 5°; after the mixture had been kept overnight at room temperature and then heated on the water-bath for 1 hour and decomposed, benzene was added and the solvent layer afforded 4 : 4′-di-*tert.*-butylbenzophenone in colourless rosettes, m. p. 133—134° (Found: C, 85·2; H, 8·8. Calc. for $C_{21}H_{26}O$: C, 85·7; H, 8·8%). Cristol *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 913) record m. p. 134—135·5° for the ketone, which was prepared from 4 : 4-di-*p-tert.*-butylstyrene. Repetition of the experiment with *m-tert.*-butylbenzoyl chloride gave impure 3 : 4′-di-*tert.*-butylbenzophenone as a pale yellow oil, b. p. 190°/1·8 mm., which did not give a solid oxime.

4 : 4′-*Di*-tert.-*butylbenzophenone oxime* was readily formed, and crystallised from alcohol in colourless prismatic needles, m. p. 195—196° (Found: C, 81·2; H, 8·3; N, 4·23. $C_{21}H_{27}ON$ requires C, 81·6; H, 8·7; N, 4·5%), which by Beckmann rearrangement gave 4 : 4′-di-*tert.*-butylbenzanilide, m. p. 156—157°.

(*b*) Carbon tetrachloride (46·2 g., 0·3 mol.) and aluminium chloride (13·3 g., 0·1 mol.) were stirred at 5° during addition of *tert.*-butylbenzene (26·8 g., 0·2 mol.) in 2 hours, kept overnight, and then treated with water. Distillation with steam removed excess of *tert.*-butylbenzene and decomposed the dichlorodiphenylmethane derivative; extraction of the residue with benzene gave 4 : 4′-di-*tert.*-butylbenzophenone, b. p. 180—190°/0·7 mm., which crystallised from alcohol in colourless prisms, m. p. 133—134°.

(*c*) 5-*tert.*-Butyl-2-*p-tert.*-butylbenzoylbenzoic acid (1·3 g.) was heated with a trace of copper bronze at 250°, and the usual procedure afforded 4 : 4′-di-*tert.*-butylbenzophenone, m. p. and mixed m. p. with the specimens prepared by methods (*a*) and (*b*), 133—134° (oxime, m. p. and mixed m. p. 195—196°).

4 : 4′-*Di*-tert.-*butylbenzanilide.*—*p-tert.*-Butylbenzoyl chloride (from 1·8 g. of acid) and *p-tert.*-butylaniline (1·5 g.) in dry benzene (4 c.c.) were refluxed for 1 hour, benzene (50 c.c.) was added, and the mixture was filtered. The filtrate gave colourless needles, m. p. 156—157°, of the *benzanilide* (Found: C, 81·7; H, 8·6; N, 4·4. $C_{21}H_{27}ON$ requires C, 81·6; H, 8·7; N, 4·5%), not depressed on admixture with the product obtained from the above Beckmann rearrangement.

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124. *Cyclitols. Part I.* iso*Propylidene Derivatives of Inositols and Quercitols. The Structure of Pinitol and Quebrachitol.*

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By the use of acetone containing zinc chloride and acetic acid, several cyclitols have been converted into *iso*propylidene derivatives. The presence of at least two contiguous hydroxyl groups in *cis*-position is necessary for reaction to occur. In the case of *epi*- and (−)-inositols, however, both di- and tri-*iso*propylidene compounds have been obtained; in the latter, contiguous hydroxyl groups in *trans*-position have reacted. The stereochemistry of these derivatives is discussed.

Pinitol gave a di*iso*propylidene, and quebrachitol a mono*iso*propylidene derivative, the latter consuming one mole of periodate. It is therefore concluded that pinitol is 3-methyl (+)-inositol, and quebrachitol is 2-methyl (−)-inositol.

In the introduction, proposals are made for the nomenclature and numbering of cyclitols.

Nomenclature and Numbering (with N. K. MATHESON).—Although the chemistry of the cyclitols has greatly expanded in the last fifteen years and there are at present many workers active in this important field (see, *e.g.*, Fletcher, *Adv. Carbohydrate Chem.*, 1948, **3**, 45), there exists neither an adequate system of nomenclature nor a generally accepted method of numbering. When naming and numbering the partially substituted cyclitols described in this paper, the lack of a system became particularly apparent; and other work in progress foreshadows further difficulties in nomenclature. In the following paragraphs therefore some rules on nomenclature and numbering are proposed; they will be used in this and in the subsequent papers of this series.

(*A*) To avoid the introduction of many new names, it is proposed that all *cyclo*hexanehexols be called inositols, all *cyclo*hexanepentols quercitols, and all pentahydroxy*cyclo*hexanones inososes, the various isomers being distinguished by prefixes. Cyclitols with

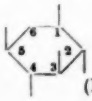
less than five hydroxyl groups will be described as derivatives of *cyclo*hexane, *e.g.*, *cyclo*hexanetetrol. The present names of inositols conform to this proposal, the only exception being scyllitol (I), for which the name *scyllo*inositol is suggested. As there is only one pair of optically active inositols, the symbols (+) and (−) describe them unequivocally.

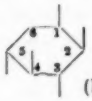
For the inososes, Posternak (*Helv. Chim. Acta*, 1942, **25**, 746) introduced a system of double prefixes, *e.g.*, *scyllo-meso*-inosose, to indicate the two inositols from which they are theoretically derivable. This proved cumbersome and many authors have dropped one of the prefixes. It is now suggested that only one prefix be used and this be the same as for the corresponding quercitols (derived by replacement of the carbonyl by a methylene group). This is already the case with *epi*quercitol (May and Mosettig, *J. Org. Chem.*, 1949, **14**, 1137) which has the same configuration as *epi*inosose (Posternak, *Helv. Chim. Acta*, 1936, **19**, 1333). Under this scheme Posternak's " desoxyscyllitol " (II) (*ibid.*, 1941, **24**, 1045), having the same configuration as *scyllo*inosose, would be called *scyllo*quercitol. Viburnitol (III) (Power and Tutin's " lævorotatory quercitol ", *J.*, 1904, **85**, 624; Hérissey and Poirot, *J. Pharm. Chim.*, 1937, [viii], **26**, 385; Posternak and Schopfer, *Helv. Chim. Acta*, 1950, **33**, 343) would be called *vibo*quercitol and the enantiomorph of the corresponding keto-compound (insufficiently named " d-inosose " by Magasanik and Chargaff, *J. Biol. Chem.*, 1948, **175**, 929) would be (+)-*vibo*inosose. For the common quercitol (IV) (" acorn sugar ") the name *proto*quercitol (πρῶτος, first) is proposed.

Derivatives of cyclitols in which other than hydroxyl groups occur but in which the asymmetry of the carbon atoms is retained, *e.g.*, inosamines (pentahydroxy*cyclo*hexylamines), bromoquercitols, are best described as derivatives of deoxy-cyclitols, *e.g.*, bromodeoxy-inositol.

(*B*) In the past nearly every worker has used a different method of numbering the cyclitols. (For a recent discussion of cyclitol numbering and for references, see Anderson and Lardy, *J. Amer. Chem. Soc.*, 1950, **72**, 3141.) Magasanik and Chargaff (*J. Biol. Chem.*, 1948, **174**, 173) have made the only attempt to introduce a logical system of numbering, but their method is contrary to the accepted usage that carbon atoms bearing functional groups should have the lowest possible numbers; and in their system the equivalent positions in enantiomorphs have different numbers. This is objectionable in principle and makes it impossible to describe racemic compounds by a single expression (see below).

(I)


(II)


(III)

(IV)

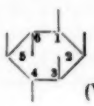
The system proposed in the following paragraphs retains the essential features of Magasanik and Chargaff's method but attempts to eliminate its weaknesses and is more generally applicable, especially to optically active compounds.

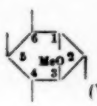
For the purposes of numbering, the *cyclo*hexane ring is regarded as a planar hexagon resulting from an imaginary flattening of the puckered ring; the directions of the valencies can then be described as " up " and " down."

Carbon atoms carrying functional groups have the lowest possible numbers, according to the accepted usage in organic chemistry. Thus, in inososes the ketonic carbon atom will be $C_{(1)}$; in quercitols the methylene group, $C_{(6)}$.

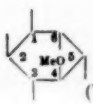
*The larger number of functional groups on one side of the plane of the hexagon shall be described by the lowest possible numbers, e.g., meso*inositol will be numbered as in (V).

If the hydrogen atom of a hydroxyl group is replaced by another group and if the above rule has not yet determined the numbering unequivocally, then this substituted position shall be given the lowest possible number, *e.g.*, pinitol will be described as 3-methyl (+)-inositol (VI) and not as 4-methyl (+)-inositol (VII).


(V)



(VI)



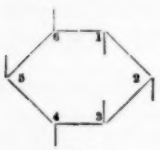
(VII)

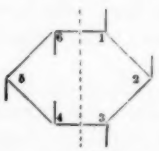
(VIII)

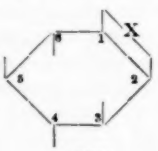
Every cyclitol can be written in two ways depending on which side is " up " and which is " down." It is proposed that the formulæ be written in such a way that the numbering is always clockwise. If, determined according to the above rules, it runs anticlockwise, *e.g.*, in formula (VIII) for (−)-*vibo*quercitol, the formula should be " turned on its back " to give (III). (+)-Inositol and (−)-inositol will then be written and numbered as in (IX) and (X), respectively; the corresponding positions have the same number (contrast Magasanik and Chargaff's method), and each carbon atom in one optical isomer has a configuration opposite to that of the same number in the other. It is further proposed that in symmetrical or racemic cyclitols, for the sake of uniformity, the lowest-numbered asymmetric carbon atom should be written with its functional group upwards, *e.g.*, (II), (XVII), (V).

(*C*) In the past, the enantiomorphs of cyclitols have been differentiated from each other by indicating the actual direction of their optical rotation. This is, obviously, a poor method because the direction of the rotation is not predictable from the structure of the compounds; it is justified only while the configuration of the enantiomorphs has not yet been determined. The configurations of most of the asymmetrical cyclitols are now known, such knowledge being, of course, not absolute but related, by degradation, to carbohydrates, *i.e.*, to the arbitrarily chosen configuration of D-glyceraldehyde. Cahn and Ingold's " sequence rule " (*J.*, 1951, 612) is unfortunately not applicable to inositols. The time therefore seems opportune for the introduction of a convention connecting the structure and the configurational symbol in an unambiguous way, as in the carbohydrate field. Proposals for such a convention have been submitted by us to this *Journal* but, at the Editor's suggestion, their publication will be deferred for further consideration and discussion. As an interim device, until a comprehensive symbolism has been devised, the enantiomorphous cyclitols will be distinguished by the (+) and (−) symbols, indicating the direction of their rotation. Compounds derived from asymmetrical cyclitols will be characterised by the symbol of the parent compound, *e.g.*, tri*iso*propylidene (−)-inositol will describe the compound made from (−)-inositol; but the symbol should not be taken to imply that the tri*iso*propylidene derivative itself is lævorotatory.

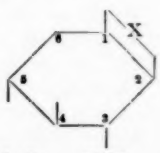
iso*Propylidene Derivatives of Cyclitols.*—The very fruitful technique of cyclic acetal formation has been extensively used in carbohydrate chemistry. In the field of the cyclitols, however, the method has been less successful. It is true that some related compounds, *e.g.*, quinic acid (H. Fischer, *Ber.*, 1921, **54**, 775), shikimic acid (Fischer and Dangschat, *Helv. Chim. Acta*, 1937, **20**, 705), conduritol (Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756), and a nitro-deoxy-inositol (Grosheintz and Fischer, *J. Amer. Chem. Soc.*, 1948, **70**, 1479), gave *iso*propylidene derivatives; but repeated attempts (Böeseken and Julius, *Rec. Trav. chim.*, 1926, **45**, 489; Karrer, *Helv. Chim. Acta*, 1926, **9**, 116; Micheel, Ruhkopf, and Suckfüll, *Ber.*, 1935, **68**, 1523) to condense *meso*inositol or *proto*quercitol with acetone or benzaldehyde failed until Dangschat (*Naturwiss.*, 1942, **30**, 146), working in collaboration with H. O. L. Fischer, reported the preparation of 1 : 2-*iso*propylidene *meso*inositol (XI) by the use of zinc chloride and acetic acid as catalyst. Only a preliminary account of this work has appeared, without experimental details; and Anderson and Wallis reported later (*J. Amer. Chem. Soc.*, 1948, **70**, 2931) that they were unable to repeat it.


(IX)


(X)



(XI)



X = $Me_2C<$ (XII)

Recently Posternak (*Helv. Chim. Acta*, 1950, **33**, 350) described the preparation of an *iso*propylidene derivative (XII) from *vibo*quercitol (III), using also a mixture of zinc chloride and acetic acid as catalyst. Following his conditions closely, we attempted the reaction of a number of cyclitols with acetone and were successful with all those compounds—including *meso*inositol—which contained at least two contiguous hydroxyl groups in *cis*-position. But there was found a great difference between the behaviour of *meso*inositol

and that of the other cyclitols. Even after prolonged heating with a large excess of acetone, zinc chloride, and acetic acid, a considerable amount of *meso*inositol remained undissolved; the other cyclitols reacted more readily: we found that the amounts of acetone and catalyst could be reduced considerably below those used by Posternak. It is apparent therefore that of the cyclitols *meso*inositol, the subject of previous attempts at acetal formation, was the least fortunate choice.

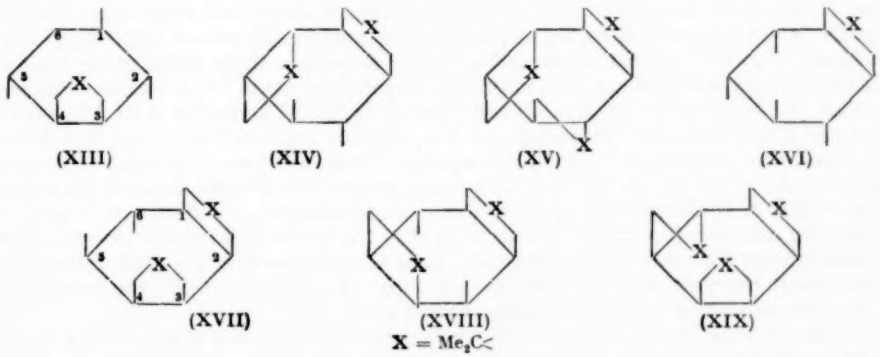
Nevertheless, the failure of Anderson and Wallis (*loc. cit.*) to condense *meso*inositol with acetone is not readily explained. Their conditions were practically the same as ours, yet after 5 days' boiling 96% of the inositol remained undissolved. Several authors (E. Fischer, *Ber.*, 1895, **28**, 2496; Freudenberg, Dürr, and Hochstetter, *ibid.*, 1928, **61**, 1735; Ohle, *ibid.*, 1938, **71**, 562) have reported that pure acetone was less suitable for such reactions than the commercial grade. Anderson and Wallis used "reagent acetone"; accordingly we made parallel runs with commercial acetone and with acetone carefully purified by permanganate oxidation and through the sodium iodide compound, but found no significant difference.

The structure of (XI) has been proved by degradation (Dangschat, *loc. cit.*), but formula (XII) was assigned by Posternak and Schopfer (*loc. cit.*) to *iso*propylidene *vibo*quercitol only on the assumption that the two hydroxyl groups in *cis*-position have reacted with acetone. Consumption of two mols. of periodate supports this structure but does not exclude the possibility of a 4 : 5-*iso*propylidene derivative. The assumption that only *cis*-hydroxyl groups will condense with acetone is based on wide experience in carbohydrate chemistry and particularly on the work of Derx (*Rec. Trav. chim.*, 1922, **41**, 318) who showed that *cis*-, but not *trans*-, 1 : 2-*cyclo*hexanediol gives an *iso*propylidene derivative. This point will be further discussed below.

It is necessary to acetylate the water-soluble *iso*propylidene compounds in order to separate them from zinc chloride. Some of the resulting acetates were not obtained in the crystalline state; but after deacetylation every *iso*propylidene derivative crystallised.

*scyllo*Inositol (I) and *scyllo*quercitol (II), two cyclitols without contiguous *cis*-hydroxyl groups, did not react with acetone. The former remained undissolved, the latter dissolved without condensing with acetone. Since the cyclitols have very low solubility in acetone, this indicates that zinc chloride increases their solubility, presumably by complex formation, which may account for part or the whole of its catalytic activity. In the case of *scyllo*quercitol, when the zinc chloride was removed by the addition of pyridine, the cyclitol was also precipitated.

*proto*Quercitol was found to give a mono*iso*propylidene derivative. As there is only one pair of contiguous *cis*-hydroxyl groups in this molecule (Posternak, *Helv. Chim. Acta*, 1932, **15**, 948), structure (XIII) is assigned to it. In agreement with this it consumed one mol. of periodate.



(−)-Inositol (X) gave two *iso*propylidene derivatives. The more soluble, also isolated as the diacetate, is a di*iso*propylidene compound. This inositol contains two pairs of *cis*-

hydroxyl groups and it is assumed that it is these which have reacted giving 1 : 2-5 : 6-di*iso*propylidene (−)-inositol (XIV); in accordance with this structure it consumes one mol. of periodate. The higher-melting, less soluble derivative could not be acetylated and was shown by analysis to be a tri*iso*propylidene derivative. In this compound two of the *iso*propylidene groups are in the same position as in (XIV) since partial hydrolysis of the former compound by dilute acetic acid gave the latter. The structure of the tri*iso*propylidene compound is therefore (XV), in which two hydroxyls in *trans*-position have condensed with the ketone. As a by-product of the hydrolysis a small amount of a mono-*iso*propylidene derivative (XVI) was isolated. It is to be noted that (−)-inositol, though dissymmetrical, has a two-fold axis of symmetry as indicated in (X); positions 1 and 6, 2 and 5, 3 and 4 are therefore equivalent, and removal of either *iso*propylidene group from (XIV) will give the same compound, 1 : 2-*iso*propylidene (−)-inositol (XVI).

The reaction of *epi*inositol with acetone is more complex. After a lengthy and wasteful separation, three crystalline products were obtained: two di- and one tri-*iso*propylidene derivatives. Of the former, the one obtained in larger amounts consumed one mol. of periodate and is therefore 1 : 2-3 : 4-di*iso*propylidene *epi*inositol (XVII); the other was not oxidised by periodate and is thus the 1 : 2-4 : 5-derivative (XVIII). Since the tri*iso*propylidene compound was converted into (XVII) by partial hydrolysis, its structure is (XIX) in which, again, two *trans*-disposed hydroxyl groups have reacted with acetone. As

FIG. 1.

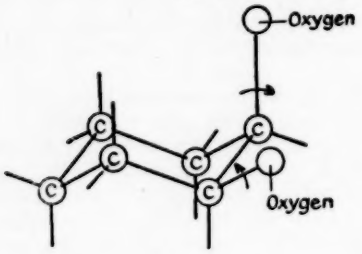
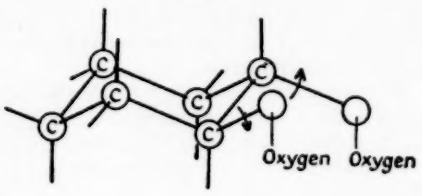


FIG. 2.



the two tri*iso*propylidene inositols are believed to be the first examples of cyclic acetal formation involving *trans*-hydroxyl groups in a *cyclo*hexane derivative, some discussion of their stereochemistry seems warranted.

The Stereochemistry of iso*Propylidene Cyclitols.*—It has been established by thermodynamical calculations (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488) and by electron-diffraction measurements (Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929) that the chair form is the most stable conformation of the *cyclo*hexane ring. In this form, three of the atoms attached to the ring carbon atoms are above, and three below, the ring ("polar" positions) whilst the other six surround the ring in an equatorial belt ("equatorial" positions) (Fig. 1). A twist of the carbon atoms through a single plane to the opposite chair form changes the polar into equatorial groups and *vice-versa*. This picture being kept in mind, the requirement of *cis*-relationship for cyclic acetal formation is far less obvious than the planar formulæ would suggest. The distance between two groups attached to adjacent carbon atoms is the same for two equatorial groups (" *trans* ") as for one equatorial and one polar (" *cis* "). In the case of hydroxyl groups, the distance between the oxygen atoms is 2·86 Å (if all valency angles on carbon are tetrahedral), a distance too large to be bridged by one carbon atom.* This explains why the cyclic acetal formation of cyclitols is more difficult than that of the open-chain sugar alcohols but does not explain the difference between the reactivity of *cis*- and *trans*-groups. To understand this, the deformation of the molecule during the reaction must be considered.

In order to bring two *cis*-disposed hydroxyl groups nearer to each other, the two carbon atoms to which they are attached will have to rotate around their connecting line as shown

* Two *trans*-situated hydroxyl groups may also be both polar, the distance between the oxygen atoms then being much larger, *viz.*, 3·66 Å.

FIG. 3. (−)-*Inositol.*

FIG. 4. *Tri*iso*propylidene* (−)-*inositol.*

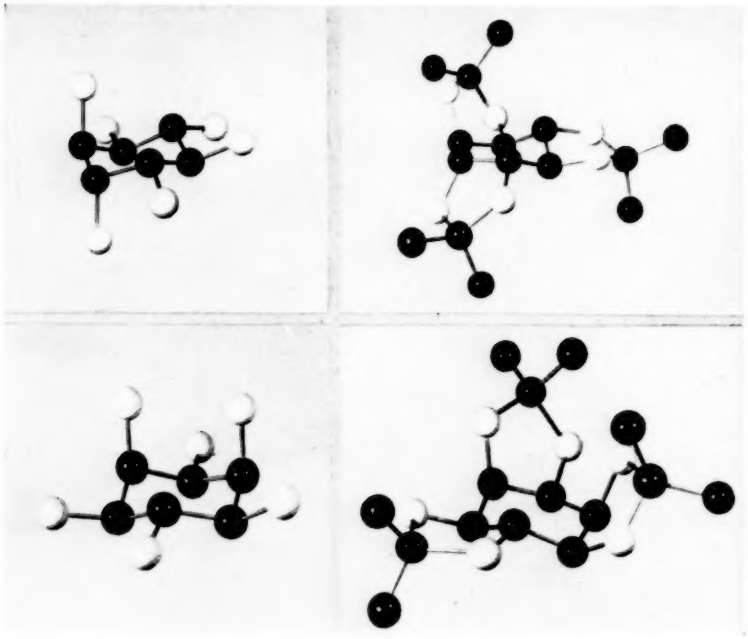


FIG. 5. epi*Inositol.*

FIG. 6. *Tri*iso*propylidene* epi*inositol.*

For clarity, only the carbon and the oxygen atoms are shown in the models.

[*To face p.* 691.

in Fig. 1. There is reason to believe that comparatively little energy is required for this rotation : the strain created is small and the interatomic repulsions are not changed to a considerable extent. This deformation makes the ring less puckered and increases the distances between the polar groups; it must be part of the process whereby one chair form is converted into the other possible chair form, a process which has a low energy of activation since isomers corresponding to the two chair forms have never been isolated.

However, when two *trans*-situated hydroxyl groups are brought nearer to each other by the rotation of the two carbon atoms according to Fig. 2, the ring becomes more puckered and two polar groups are moved nearer to the other polar groups. Very considerable energy will be required for this movement because the distance between the polar groups (2·51 Å), even if they are all hydrogen atoms, is not much larger than the sum of their van der Waals radii. If one of the polar groups is larger than hydrogen the van der Waals radii will touch or even overlap. The energy required to bring the polar groups nearer to each other (cf. the " compression energy," Ingold and Hughes, *J.*, 1946, 157 *et seq.*) will be large and it can be said that the rotation which brings the *trans*-situated hydroxyl groups into a plane is sterically hindered.

The situation is different, however, in the di*iso*propylidene compounds. Formation of two acetal rings from two pairs of *cis*-hydroxyl groups has moved four of the polar groups nearer to the equatorial belt. Their distances from the remaining two polar groups have been increased and, accordingly, the hindrance towards the rotation shown in Fig. 2 has been considerably lessened and acetal formation becomes possible. We conclude that, in agreement with the experimental findings, acetone will condense with a pair of *trans*-hydroxyl groups of a *cyclo*hexane ring only if two *cis*-pairs have already thus reacted. Even then the *trans*-hydroxyl groups react more slowly than the *cis*-groups, as shown by the fact that mixtures of di- and tri-*iso*propylidene derivatives were always obtained.

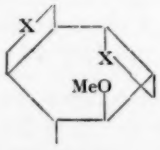
Models of (−)-inositol and of its tri*iso*propylidene derivative are shown in Figs. 3 and 4. In the former, all valency angles are tetrahedral; comparison of the two models shows clearly how the polar hydroxyl groups have been displaced in Fig. 4 (the polar valencies are no longer vertical) and how that part of the six-carbon ring which contains the *cis*-hydroxyl groups has been flattened whilst the other part has been more strongly puckered. Figs. 5 and 6 show a similar comparison between *epi*inositol and its tri*iso*propylidene derivative.

There is another possibility which cannot be overlooked (cf. Derx, *loc. cit.*) : that in the mono*iso*propylidene derivatives the *cyclo*hexane ring is in its boat form. In this form two pairs of carbon atoms, on the opposite side of the " boat," are in eclipsed conformation, *i.e.*, the two carbon atoms and two *cis*-groups attached to them lie in one plane. Cyclic acetal formation can occur, therefore, without deformation. It is to be noted, however, that the boat form has a markedly higher energy than the chair form because of its shorter distances between some of the non-bonded atoms. From our work, the following argument can be advanced against the boat form of *iso*propylidene cyclitols : Mono*iso*propylidene *epi*inositol, in its boat form, would have a *cis*-pair of hydroxyl groups opposite the acetal ring in a favourable position for the formation of another acetal ring. Further reaction should therefore give mainly the 1 : 2-4 : 5-di*iso*propylidene compound; in fact, however, the 1 : 2-3 : 4-derivative (and the triacetal derived from it) was formed predominantly.

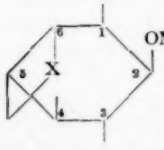
It should be mentioned that 1 : 3-*cis*-hydroxyl groups, when in the polar position, are favourably situated for acetal formation. The distance between them is 2·51 Å if all the inter-bond angles are tetrahedral. This is less than double the van der Waals radius of oxygen, and it is probable therefore that this distance has been increased by mutual repulsion unless there is a hydrogen bond between them.* Such a pair of 1 : 3-*cis*-hydroxyl groups in polar positions exists in *epi*inositol; reaction of these with acetone would give a mono-*iso*propylidene derivative incapable of further condensation. Such a derivative has not been encountered in our work.

* The question whether there is a hydrogen bond between 1 : 3-*cis*-hydroxyl groups in polar positions has been investigated by Drs. Rees and Willis (Commonwealth Scientific and Industrial Research Organisation, Melbourne) by comparison of the infra-red spectra of the *cis*- and *trans-cyclo*hexane-1 : 3-diols, and of *meso*- and *epi*-inositol. The results, however, were inconclusive (private communication).

The Structure of Pinitol and Quebrachitol.—Pinitol, a monomethyl ether of (+)-inositol, which occurs in various conifers, particularly in *Pinus lambertiana* Dougl., gave a di*iso*propylidene derivative. This indicates that the methyl group is not on any of the two pairs of *cis*-oxygen atoms; and as the remaining two positions are equivalent, pinitol must be 3-methyl (+)-inositol (VI), and the diacetal is 3-methyl 1 : 2-5 : 6-di*iso*propylidene (+)-inositol (XX).



(XX)



(XXI)

Quebrachitol, a monomethyl ether of (−)-inositol, which occurs in the latex of *Hevea brasiliensis* and in several other plants, is not the enantiomorph of pinitol. The methoxyl group can therefore be only on carbon atoms 1 or 2 (carbon atoms 5 and 6 being equivalent to these). It gave a mono*iso*propylidene compound which consumed only one mol. of periodate; therefore the acetal is 2-methyl 5 : 6-*iso*propylidene (−)-inositol (XXI) and quebrachitol is 2-methyl (−)-inositol.

It is interesting to consider these compounds in the light of their possible biogenesis. It is widely believed that inositols are formed in nature by ring closure of *aldo*hexoses (Fischer, Harvey Lectures, 1944—45, **40**, 174). If such closure gave a methyl inositol the most probable position of the methyl group would be on that carbon atom which was aldehydic in the sugar. Amongst the naturally occurring *aldo*hexoses, D-glucose and D-galactose can give (−)-inositol on ring closure; and, if a methyl group entered the glycosidic hydroxyl group, quebrachitol would be formed in both cases. Similarly, (+)-inositol could be produced from D-mannose and from D-galactose; the methyl inositol formed by methylation on the glycosidic carbon atom would be pinitol in both cases.

Experimental

M. p.s, which are corrected, were taken, unless otherwise stated, by placing the intact crystals on a heated aluminium block. The rotations were determined in a 2 dm.-tube. Microanalyses were carried out in this Department by Mrs. E. Bielski.

Materials.—*meso*Inositol and (+)-*proto*quercitol were commercial preparations. Crude pinitol was obtained through the courtesy of Dr. Arthur B. Anderson, Oregon Lumber Co., Portland, U.S.A. It was purified by treating its aqueous solution with charcoal and adding ethanol to the concentrated solution. Crude quebrachitol was kindly presented to us by Mr. M. W. Philpott, The Rubber Research Institute of Malaya, Kuala Lumpur. It was purified in the same way as the pinitol. (−)-Inositol was obtained by demethylation of quebrachitol with hydriodic acid. (−)-*vibo*Quercitol was isolated in this Department from *Stephania hernandifolia*, Walp., by Mrs. J. Ewing (Ewing, Hughes, and Ritchie, *Austral. J. Sci. Res.*, *A*, 1950, **3**, 514). *scyllo*Inositol and *scyllo*quercitol were prepared by catalytic hydrogenation of *scyllo*inosose (Posternak, 1941, *loc. cit.*), and *epi*inositol by the hydrogenation of *epi*inosose (Posternak, *Helv. Chim. Acta*, 1946, **29**, 1996). The acetone was a commercial grade, made by fermentation, free from reducing impurities; it was kept over anhydrous potassium carbonate.

Reaction of meso*Inositol with Acetone.*—Finely powdered anhydrous *meso*inositol (2·0 g.), anhydrous zinc chloride (24 g.), acetic acid (24 ml.), and dry acetone (180 ml.) were heated under reflux for 9 hours. After the undissolved inositol (1·51 g.) had been filtered off, dry pyridine (90 ml.) was added to the solution, the precipitated complex salt was filtered off after a few hours, and the acetone was removed under reduced pressure at 40°. Acetic anhydride (30 ml.) and dry pyridine (50 ml.) were added to the residue; on the following day a further amount of complex salt was filtered off and washed with a small amount of ice-cold chloroform. More chloroform (15 ml.) was added to the filtrate which was then shaken with iced water (2 × 50 ml.), sodium carbonate solution (2 × 50 ml.; 5%), and again with iced water (2 × 10 ml.). The chloroform layer was dried (Na_2SO_4) and evaporated, and the residue crystallised from ethyl acetate–light petroleum to obtain (±)-3 : 4 : 5 : 6-tetra-acetyl 1 : 2-*iso*propylidene *meso*-inositol (0·5 g.; 47% on inositol not recovered), m. p. 118—121°.

This compound (0·33 g.) was heated under reflux for 10 minutes with anhydrous methanol (6 ml.) containing 1 millimole of sodium methoxide. After the solvent had been removed, crystallisation of the residue from ethanol (4 ml.) gave (±)-1 : 2-*iso*propylidene *meso*inositol (0·12 g., 64%), m. p. 182—183° (Found : C, 48·95; H, 7·25. Calc. for $C_9H_{16}O_6$: C, 49·1; H, 7·35%). Dangschat (*loc. cit.*) reports m. p. 182—183°.

It was of interest to determine the amount of periodate consumed by this compound which has four contiguous hydroxyl groups, since anomalous results were obtained with compounds containing five (Hérissey and Poirot, *loc. cit.*; Riggs, *J.*, 1949, 3199) and six (Fleury, Poirot, and Fievet, *Compt. rend.*, 1945, **220**, 664) hydroxyl groups attached to a *cyclo*hexane ring. From a solution of *iso*propylidene *meso*inositol (22·0 mg. , 0·1 millimole) and sodium meta-periodate (0·75 millimole) in water (25 ml.), kept in the dark, aliquots (5 ml.) were taken at intervals, sodium hydrogen carbonate solution (2 ml.; M.), sodium arsenite solution (15·0 ml.; 0·025N.), and potassium iodide (0·1 g.) were added and, after 5 minutes, the solution was titrated with 0·025N-iodine solution. The results, expressed in moles of periodate consumed per mole of *iso*propylidene inositol were : 0·5 hour, 1·96; 1 hour, 2·18; 2 hours, 2·40; 15 hours, 2·72.

Reaction of (+)-proto*Quercitol with Acetone.*—Finely powdered *proto*quercitol (2 g.), anhydrous zinc chloride (10 g.), acetic acid (10 ml.), and dry acetone (80 ml.) were heated under reflux for 5 hours. The cyclitol dissolved in about 30 minutes. To the cooled mixture dry pyridine (20 ml.) was added to precipitate most of the zinc chloride as a complex salt; after cooling to 0°, the crystals were filtered off and washed with acetone (10 ml.). The mother-liquor was freed from acetone under reduced pressure at 40° and acetic anhydride (10 ml.) was added. After 24 hours the mixture was cooled to 0° and filtered, and the salt washed with ice-cold chloroform (10 ml.). After the addition of more chloroform (20 ml.), the filtrate was repeatedly shaken with 30-ml. portions of iced water until the aqueous layer no longer showed a reaction for zinc with potassium ferrocyanide (4—5 times). The combined aqueous layers were shaken with chloroform (15 ml.) which was then washed with water (15 ml.) and combined with the bulk of the chloroform solution. After further washings with sodium carbonate solution (2 × 10 ml.; 5%) and water (10 ml.), the chloroform layer was dried (Na_2SO_4) and evaporated.

The residue (2·94 g.) was a syrup which could be distilled without decomposition at 130° (bath-temp.)/0·3 mm., but did not crystallise. Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave **3** : 4-iso*propylidene* (+)-proto*quercitol* (1·1 g., 44%), m. p. 158°. For analysis it was recrystallised from ethyl acetate and then had m. p. 159° and $[\alpha]_D^{20}$ + 73·7° (*c*, 1·2 in ethanol) (Found : C, 52·9; H, 7·95. $C_9H_{16}O_6$ requires C, 52·95; H, 7·9%).

Periodate oxidations. In determining the amount of periodate consumed by this compound, we at first reduced the excess of periodate with iodide and titrated the liberated iodine with arsenite. Erratic results, varying between 1 and 2 mols., were thus obtained. It is suspected that the oxidation product reacts with iodine, probably by the iodoform reaction (quercitols give the iodoform reaction). Consistent results were obtained, however, when the unchanged periodate was reduced by excess of arsenite in the presence of iodide—no free iodine being then present in the solution—and the excess of arsenite was titrated by an iodine solution as described under *meso*inositol (Method A). Thus, aliquots from a solution of *iso*propylidene *proto*quercitol (81·6 mg., 0·4 millimole) and sodium metaperiodate (0·9 millimole) in water (25 ml.) gave the following results : 0·5 hour, 1·01; 1 hour, 1·02; 4 hours, 1·04 mols. With most of the other *iso*propylidene derivatives, however, the simple titration of the liberated iodine by arsenite (Method B) gave consistent results.

Reaction of scyllo*Inositol with Acetone.*—Treated under the conditions described for *proto*quercitol, *scyllo*inositol remained completely undissolved.

Reaction of scyllo*Quercitol with Acetone.*—When *scyllo*quercitol (0·49 g.) was treated as described under *proto*quercitol, 0·29 g. did not dissolve. Evaporation of the chloroform solution gave only 0·05 g. of material. The rest of the quercitol was found in the zinc chloride–pyridine complex (4·7 g.); by acetylation with acetic anhydride (2·5 ml.) and pyridine (2·5 ml.) and working up as usual, penta-acetyl *scyllo*quercitol (0·27 g.), m. p. 193—194°, was obtained. Posternak (1942, *loc. cit.*) reports m. p. 190°.

Reaction of (−)-vibo*Quercitol with Acetone.*—When *vibo*quercitol was treated as described under *proto*quercitol, crystallisation from aqueous ethanol gave a 60% yield of **3** : **4** : 5-triacetyl **1** : 2-*iso*propylidene (−)-*vibo*quercitol, m. p. 104° (Posternak, 1950, *loc. cit.*).

Reaction of (−)-*Inositol with Acetone.*—When (−)-inositol (2 g.) was treated as described under *proto*quercitol, evaporation of the chloroform solution gave 4·6 g. of a semi-solid material. Crystallisation from ethanol (8 ml.) yielded **1** : 2-**3** : 4-**5** : 6-*tri*iso*propylidene* (−)-*inositol* (1·0 g., 30%), m. p. 211°. For analysis it was recrystallised from ethanol and then had m. p. 213—

214° (capillary), $[\alpha]_D^{25}$ + 38·1° (*c*, 1·0 in chloroform) (Found : C, 59·85; H, 8·2. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·05%).

The mother-liquor of the triacetal was evaporated and the residue crystallised twice from ethanol–water (1 : 2) : needles of 3 : 4-*diacetyl* 1 : 2-5 : 6-*di*iso*propylidene* (−)-*inositol* (1·65 g., 43%), m. p. 126°, were obtained. Another crystallisation raised the m. p. to 129°, $[\alpha]_D^{22}$ −116·5° (*c*, 2·1 in chloroform) (Found : C, 55·55; H, 7·05. $C_{16}H_{24}O_8$ requires C, 55·8; H, 7·0%).

Catalytic deacetylation, followed by crystallisation from ethyl acetate–light petroleum (2 : 1), gave 1 : 2-5 : 6-*di*iso*propylidene* (−)-*inositol*, m. p. 153°, $[\alpha]_D^{20}$ −4·7° (*c*, 1·2 in ethanol) (Found : C, 55·25; H, 7·85. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). Periodate oxidation (Method B) : 0·4 millimole (104·0 mg.), and 0·6 millimole of sodium metaperiodate in water (25 ml.) : 1 hour, 1·01; 2 hours, 1·01; 4 hours 1·01 mols.

Partial Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tri*iso*propylidene* (−)-*Inositol*.—A solution of tri*iso*propylidene (−)-inositol (0·7 g.) in a mixture of chloroform (3·0 ml.), acetic acid (3·5 ml.), and water (1·0 ml.) was set aside for 24 hours and then was evaporated to dryness under reduced pressure. The residue was extracted with water, leaving unchanged triacetal (0·12 g., m. p. after recrystallisation from ethanol, 208—210°) undissolved. The aqueous extract was evaporated to dryness under reduced pressure and extracted with ethyl acetate (2 × 5 ml.) which left impure (−)-inositol (0·04 g.) undissolved. The extracts were evaporated and the residue re-extracted with benzene (20 ml.); the undissolved 1 : 2-iso*propylidene* (−)-*inositol* (50 mg., 10%), after recrystallisation from ethyl acetate (1 ml.), had m. p. 157·5—158° (Found : C, 49·5; H, 7·4. $C_9H_{16}O_6$ requires C, 49·1; H, 7·35%).

The benzene solution, on cooling, deposited 1 : 2-5 : 6-di*iso*propylidene (−)-inositol (0·25 g., 41%), m. p. 149—150°, mixed m. p. with an authentic sample, 150—151°.

Reaction of epi*Inositol with Acetone*.—When *epi*inositol (4 g.) was treated as described under *proto*quercitol, evaporation of the chloroform solution yielded 7·9 g. of an oil. Crystalline acetates can be obtained from this oil but their separation is difficult. Therefore the oil was catalytically deacetylated and then taken up in chloroform (10 ml.) which was repeatedly extracted with water (25, 10, 10 ml.). The combined aqueous layers were shaken with chloroform (5 ml.) and this with water (5 ml.). The combined chloroform layers were evaporated and the residue (1·0 g., 15%) was recrystallised several times from light petroleum, to give (±)-1 : 2-3 : 4-5 : 6-*tri*iso*propylidene* epi*inositol* (Found : C, 59·55; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·05%). It melted at 121°, resolidified and melted again at 127—128°. This compound, in contrast to tri*iso*propylidene (−)-inositol, is soluble in water.

The combined aqueous layers were evaporated, and the residue was extracted with ethyl acetate (30, 15, 15 ml.). The extracts were concentrated to 15 ml. and on storage at 0° deposited impure (±)-1 : 2-3 : 4-*di*iso*propylidene* epi*inositol* (1·85 g., 32%), m. p. about 176°. (Mother-liquor : see below.) Repeated crystallisation from ethyl acetate gave the pure compound, m. p. 181° (Found : C, 55·15; H, 7·95. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). Periodate oxidation (Method B) : 0·2 millimole (52·0 mg.) and 0·5 millimole of sodium periodate in water (25 ml.) : 0·5 hour, 1·01; 1 hour, 1·01; 2 hours, 1·01 mols.

Acetylation of this compound with acetic anhydride and pyridine gave (±)-5 : 6-*diacetyl* 1 : 2-3 : 4-*di*iso*propylidene* epi*inositol* which crystallised from ethanol in fine needles, m. p. 138° (Found : C, 55·45; H, 7·2. $C_{16}H_{24}C_8$ requires C, 55·8; H, 7·0%).

The mother-liquor from 1 : 2-3 : 4-di*iso*propylidene *epi*inositol (see above) was evaporated to dryness and heated for 1 hour on the steam-bath with acetic anhydride (4 ml.) and pyridine (4 ml.). It was then poured into water and extracted with chloroform (3 × 8 ml.). After evaporation of the solvent and crystallisation from light petroleum (200 ml.), crude 3 : 6-*diacetyl* 1 : 2-4 : 5-*di*iso*propylidene* epi*inositol* (0·43 g., 5·5 %), m. p. 187—192°, was obtained. Repeated crystallisation from light petroleum gave the pure compound, m. p. 201—203° (Found : C, 55·65; H, 6·95. $C_{16}H_{24}O_8$ requires C, 55·8; H, 7·0%).

Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave 1 : 2-4 : 5-*di*iso*propylidene* epi*inositol*, m. p. 181° (Found : C, 54·9, 55·75; H, 7·8, 7·9. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). The mixed m. p. with 1 : 2-3 : 4-isomer (m. p. also 181°) was depressed by more than 10°. This compound did not reduce sodium metaperiodate under the usual conditions.

This separation of the di*iso*propylidene isomers is unsatisfactory and will be further studied.

Partial Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tri*iso*propylidene* epi*Inositol*.—On being kept for 24 hours, a solution of tri*iso*propylidene *epi*inositol (0·39 g.) in a mixture of acetic acid (2·0 ml.) and water (0·5 ml.) deposited prisms of *epi*inositol (0·13 g., 56%), m. p. 303—304°. This m. p. is higher than that of our initial *epi*inositol, m. p. 297—298°. Posternak (*Helv. Chim. Acta*,

1936, **19**, 1340) records m. p. 285° (uncorr.; capillary); but because of decomposition we found it impossible to observe a definite m. p. in the capillary.

The mother-liquor was evaporated to dryness under reduced pressure and was extracted with ethyl acetate (4 ml.). On cooling, (±)-1 : 2-3 : 4-di*iso*propylidene *epi*inositol (50 mg., 15%), m. p. and mixed m. p. 181°, crystallised.

Reaction of Pinitol with Acetone.—When pinitol (2 g.) was treated as described for *proto*quercitol, evaporation of the chloroform solution gave a syrup (3·4 g.) which failed to crystallise. Catalytic deacetylation, followed by two crystallisations from light petroleum, gave *3-methyl 1 : 2-5 : 6-diisopropylidene (+)-inositol* (1·8 g., 64%), m. p. 99—100°. Further crystallisations raised the m. p. to 103—104°, $[\alpha]_D^{23}$ −22·0° (*c*, 3·4 in water) (Found: C, 56·95; H, 8·0. $C_{13}H_{22}O_6$ requires C, 56·85; H, 8·05%).

Reaction of Quebrachitol with Acetone.—When quebrachitol (2 g.) was treated as described for *proto*quercitol, evaporation of the chloroform solution gave a syrup (2·7 g.) which failed to crystallise. Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave *2-methyl 5 : 6-isopropylidene (−)-inositol* (0·55 g., 22%), m. p. 131—132°. Further crystallisation raised the m. p. to 134—135·5°, $[\alpha]_D^{23}$ −88·8° (*c*, 1·6 in water) (Found: C, 51·0; H, 7·65. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75%). Periodate oxidation (Method A): 0·4 millimole (93·6 mg.) and 0·9 millimole of sodium metaperiodate in water (25 ml.): 0·5 hour, 1·01; 1 hour, 1·01; 2 hours, 1·01; 4 hours, 1·03 mols.

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125. *Cyclitols. Part II.* Dipole Moments of Some Cyclitol Acetates.*

By C. L. ANGYAL and S. J. ANGYAL.

The electric dipole moments of several fully acetylated inositols, quercitols, and inositol methyl ethers have been measured in solution. The correlation between configuration and dipole moments is discussed.

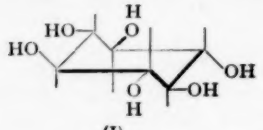
THE dipole moments of the isomeric benzene hexachlorides have been the subject of much work and discussion in recent years (Melander, *Svensk. Kem. Tids.*, 1946, **58**, 231; Hetland, *Acta Chem. Scand.*, 1948, **2**, 678; Jatkar and Kulkarni, *Science and Culture*, 1949, **14**, 482; Rolla, Fontana, and Marinangeli, *Gazzetta*, 1949, **79**, 491; Bastiansen, Ellefsen, and Hassel, *Research*, 1949, **2**, 248; Lind, Hobbs, and Gross, *J. Amer. Chem. Soc.*, 1950, **72**, 4474). It seemed of interest therefore to make similar measurements on the inositols, since they constitute the only other group of hexasubstituted *cyclo*hexanes in which the configuration of a number of isomers is known. Of the eight possible inositols, four (I—IV) † were available for measurements, two others (*allo*- and *muco*-inositol; Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756) are not well known, and the remaining two are yet unknown. For comparison a number of related compounds (V—VIII) were included in the measurements. Since the cyclitols are completely insoluble in non-polar solvents their fully acetylated derivatives were used.

It was realised that rigorous calculations of the dipole moments from the known structures and configurations would not be possible for two reasons. First, free rotation of acetyl groups around the C–O bond makes the direction of the moment of each acetyl group uncertain; and, secondly, deviations from the tetrahedral angles will occur because of the mutual repulsion of the acetyl groups. The first difficulty only was encountered by Everard and Sutton (*J.*, 1951, 16) in their attempt to evaluate the dipole moment of hexamethoxybenzene, yet the case was regarded as too complicated for rigorous treatment. On the other hand, no difficulty arises from free rotation in the benzene hexachlorides but it has been shown (Bastiansen, Ellefsen, and Hassel, *Acta Chem. Scand.*, 1949, **3**, 918) that

* Part I, preceding paper.

† The formulæ (I—VIII) are approximate perspective representations of chair forms; the heavy lines are to be visualised as in front of the plane of the paper. Slight distortion of the bonds is involved, but polar and equatorial bonds are clearly distinguished. Editors of other journals may like to note that only 45° and 90° angles are involved.—ED.

the mutual repulsion of chlorine atoms causes deflections from the tetrahedral angles and therefore the actual moments are much smaller than those calculated (Lind *et al.*, *loc. cit.*). Nevertheless it was expected that the dipole moments of the inositol acetates would at least be in the expected sequence and this was verified by the measurements. Thus determinations of the dipole moments may be useful for the establishment of yet unknown configurations; in particular, they were to have been applied in the case of pinitol and quebrachitol, two inositol methyl ethers; but in the meanwhile their configuration was determined by purely chemical methods (cf. preceding paper).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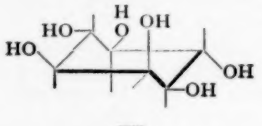
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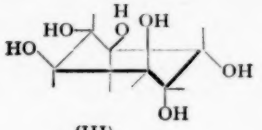
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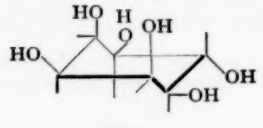
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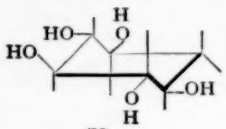
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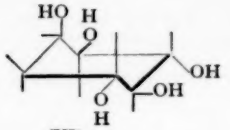
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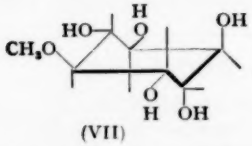
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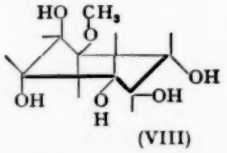
(VIII)

In order to discuss the results it must be realised that in the most stable conformation of the *cyclo*hexane ring—the chair form—the substituent groups are either in "polar" (*p*) or in "equatorial" (*e*) position (cf. the discussion and Fig. 1 in the preceding paper). The formulæ (I—VIII) are written in a way which shows these relations. In the following Table the equatorial-polar disposition † of the acetoxy-groups is given for each cyclitol, together with the measured dipole moment. The nomenclature used is that proposed in the preceding paper.

Hexa-acetate of	Acetoxy-groups						μ, D	Penta-acetate of	Acetoxy-groups						μ, D
*scyllo*Inositol (I)	*e*	*e*	*e*	*e*	*e*	*e*	2·3	*scyllo*Quercitol (V).....	*e*	*e*	*e*	*e*	*e*	–	2·3
*meso*Inositol (II)	*e*	*p*	*e*	*e*	*e*	*e*	2·8	(−)-*vibo*Quercitol (VI)	*p*	*e*	*e*	*e*	*e*	–	2·3
(±)-Inositol (III)	*p*	*e*	*e*	*e*	*e*	*p*	3·0	Pinitol (VII)	*p*	*e*	*e**	*e*	*e*	*p*	4·1
*epi*Inositol (IV)	*e*	*p*	*e*	*p*	*e*	*e*	4·1	Quebrachitol (VIII) ...	*p*	*e**	*e*	*e*	*e*	*p*	3·3

* Methoxy-group.

Discussion.—*scyllo*Inositol, being centrosymmetrical, should have no moment but for the free rotation of the acetoxy-groups; the corresponding benzene hexachloride (β) has a moment of zero. It is interesting to compare our result with the value of 2·05 observed for hexamethoxybenzene (Everard and Sutton, *loc. cit.*). Introduction of one group into the polar position increases the moment; two acetoxy-groups in polar positions on the opposite sides of the ring cause a further slight increase. The corresponding benzene hexachlorides (δ and α) both have moments of 2·2 D. Introduction of two polar groups on the same side of the ring results in a further considerable increase in polarity; the corresponding benzene hexachloride is not known.

It is remarkable that the quercitols, though less symmetrical, have moments not larger

† The *e*-*p* disposition is readily obtained from the conventional planar formulæ (as shown in the preceding paper) if it is realised that two adjacent "*trans*"-groups are both *e* or both *p*, and of two adjacent "*cis*"-groups one is *e* and one is *p*. For each molecule two chair forms are possible of which the one containing fewer substituents in polar positions is regarded as the more stable (Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929) and is given here.

than that of *scyllo*inositol. This probably indicates that the acetoxy-groups orient themselves so as to fill in the space available near the methylene group. Replacement of an acetoxy- by a methoxy-group reduces the symmetry of the molecule and therefore increases the polarity but the influence of the position of the group is not understood.

Experimental

Materials.—The cyclitols were obtained as described in the preceding paper. They were acetylated by heating them with acetic anhydride containing a trace of sulphuric acid. Their m. p.s were in agreement with the values recorded in the literature. Hexa-acetyl (±)-inositol was obtained by mixing equal parts of the (+)- and the (−)-compound, made from pinitol and quebrachitol, respectively.

Measurements.—Details of procedure and calculation were as recorded by Calderbank and Le Fèvre (*J.*, 1948, 1949; cf. also Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1). Benzene was used as a solvent except for hexa-acetyl *scyllo*inositol. Some of the compounds (II, IV, V) are insufficiently soluble in cold benzene; they were dissolved by warming them and then remained in solution at 25°. Hexa-acetyl *scyllo*inositol is insoluble in benzene; it dissolved in warm dioxan but tended to crystallise slowly at 25°, thereby reducing the accuracy of the determination. The measurments, made at 25°, are tabulated below under the usual headings (Calderbank and Le Fèvre, *loc. cit.*).

10^4w_1	ε^{25}	d_4^{25}	$a\varepsilon_2$	β
0	2·2725	0·87378	—	—
Hexa-acetyl meso*inositol.*				
8 831	2·2888	0·87602	1·846	0·2902
12 269	2·2947	0·87692	1·809	0·2929
13 980	2·2978	0·87738	1·810	0·2947
Whence $a\varepsilon_2$ = 1·82 (mean); β = 0·293 (mean).				
Hexa-acetyl (±)-*inositol.*				
10 624	2·2953	0·87649	2·146	0·2919
15 612	2·3063	0·87768	2·165	0·2859
21 169	2·3190	0·87914	2·192	0·2898
Whence $a\varepsilon_2$ = 2·17 (mean); β = 0·289 (mean).				
Penta-acetyl (−)-vibo*quercitol.*				
11 410	2·2880	0·87621	1·358	0·2437
17 001	2·2953	0·87677	1·341	0·2020
22 759	2·3026	0·87880	1·323	0·2524
Whence $a\varepsilon_2$ = 1·34 (mean); β = 0·233 (mean).				
Penta-acetyl quebrachitol.				
10 495	2·3027	0·87639	2·877	0·2846
14 924	2·3156	0·87751	2·888	0·2860
20 832	2·3323	0·87868	2·871	0·2692
Whence $a\varepsilon_2$ = 2·88 (mean); β = 0·280 (mean).				

10^4w_1	ε^{25}	d_4^{25}	$a\varepsilon_2$	β
Hexa-acetyl epi*inositol.*				
10 692	2·3174	0·87655	4·199	0·2965
14 092	2·3310	0·87757	4·151	0·3077
17 949	2·3460	0·87834	4·095	0·2907
Whence $a\varepsilon_2$ = 4·15 (mean); β = 0·298 (mean).				
Penta-acetyl scyllo*quercitol.*				
3466	2·2377	0·87477	1·486	0·3268
5194	2·2798	0·87517	1·405	0·3063
7193	2·2823	0·87564	1·362	0·2960
Whence $a\varepsilon_2$ = 1·42 (mean); β = 0·310 (mean).				
Penta-acetyl pinitol.				
9 926	2·3164	0·87622	4·423	0·2813
14 884	2·3385	0·87727	4·435	0·2684
19 377	2·3584	0·87858	4·433	0·2835
Whence $a\varepsilon_2$ = 4·43 (mean); β = 0·278 (mean).				
Hexa-acetyl scyllo*inositol* (*in dioxan*).				
0	2·2184	1·0296	—	—
1468	2·2202	1·0297	1·226	0·068
3021	2·2221	1·0301	1·225	0·115
4205	2·2235	—	1·213	—
6086	2·2259	1·0300	1·232	0·064
Whence $a\varepsilon_2$ = 1·22 (mean); β = 0·08 (mean).				

Calculation of results.

Acetate of	*M.*	$a\varepsilon_2$	β	$_\infty P_T$	$[R_L]_D$	μ, D
*meso*Inositol	432·4	1·82	0·293	252·4	93·0	2·79
*epi*Inositol	432·4	4·15	0·298	440·8	93·0	4·12
(±)-Inositol	432·4	2·17	0·289	281·1	93·0	3·03
*scyllo*Quercitol	374·3	1·42	0·310	188	82·1	2·28
(−)-*vibo*Quercitol	374·3	1·34	0·233	192·3	82·1	2·32
Pinitol	404·4	4·43	0·278	436·5	88·4	4·13
Quebrachitol	404·4	2·88	0·280	318·2	88·4	3·35
*scyllo*Inositol	432·4	1·22	0·08	198	93·0	2·3

The authors are indebted to Dr. Arthur B. Anderson, Oregon Lumber Co., Portland, U.S.A., and to Mr. M. W. Philpott, The Rubber Research Institute of Malaya, Kuala Lumpur, for samples of pinitol and quebrachitol, respectively. One of them (C. L. A.) thanks Professor R. J. W. Le Fèvre for helpful discussions. Financial assistance from the Commonwealth Science Fund is gratefully acknowledged.

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126. *The Kinetics of the Dissolution of Zinc in Aqueous Iodine Solutions. Part III.**

By A. C. Riddiford and L. L. Bircumshaw.

Zinc, copper, amalgamated copper, brass, lead, and nickel dissolve in aqueous iodine solutions at the same rate under the same experimental conditions. The observed rate of dissolution of zinc is independent of the crystal face exposed to attack, but is a function of the rate of stirring and is higher on the leading edges of the specimen than on the trailing edges. The results are in agreement with Levich's theory. It is concluded that the observed rate is determined solely by the rate of transport of iodine to the metal surface.

On the basis of experimental results reported in Parts I and II (*J.*, 1951, 598, 1490) it was concluded that the observed rate of dissolution of zinc in aqueous iodine solutions is at least partly determined by the rate of transport of iodine to the metal surface, and that it is independent of the rate of recession of products from the surface, under the conditions studied. The experiments described in this paper were designed to find whether the rate of chemical reaction at the surface makes any contribution to the observed rate of dissolution. The following points have been investigated: (1) The rate of dissolution of certain other metals in aqueous iodine solutions; (2) the rate on different crystal faces of the zinc specimen; (3) the influence of the rate of stirring; (4) the variation in the observed rate on the leading and the trailing edges of the specimen.

Experimental

The apparatus and experimental method have been described (Part I, *loc. cit.*). The solutions were initially N/25 in iodine and N/100 with respect to sulphuric acid. The temperature was 25° ± 0·01°. Except where otherwise stated, the rate of stirring was 100 r.p.m.

Rate of Dissolution of Other Metals.—The rate of dissolution of copper in a solution of standard composition (4N/25-potassium iodide), and of copper, amalgamated copper, brass, lead, and nickel-foil specimens in solutions 4N. with respect to potassium iodide, was studied. The copper,

Table 1.

Metal	Concn. of KI, moles/l.	k_1 (obs.)*	Metal	Concn. of KI, moles/l.	k_1 (obs.)*
Copper	0·16	0·113,† 0·114 †	Lead	4·0	0·163 †
Copper	4·0	0·165	Nickel	4·0	0·164, 0·164
Amalgamated copper	4·0	0·165	Zinc	4·0	0·164
Brass	4·0	0·166			

* Here and throughout, k_1 is given in the units cm. min.$^{-1}$ † Initial value.

lead, and nickel foil were of high purity. The copper and lead were supplied by I.C.I. Metals Ltd., through the courtesy of Dr. Maurice Cook. The brass sample was not analysed. The observed values of k_1, the rate constant per unit area at unit volume, are recorded in Table 1; the corresponding value for zinc foil (Table I, Part II) has been included for comparison. In the case of copper in the 4N/25-potassium iodide solution, and of lead, a fall-off in the observed rate occurred after 15 min. This effect was traced to the separation of solid cuprous and lead iodides, respectively, neither of which adhered firmly to the metal surface: initial values of k_1 are therefore recorded for these runs.

Rate on Different Crystal Faces.—To determine whether the observed rate varies on different faces, two cast-zinc cylinders were used. In one, the crystal *c* axes were orientated parallel to the axis of the cylinder, in the other, radially. The cylinders were carefully machined to the required dimensions such that the curved surface was equal in area to a standard size specimen, drilled along the axis, mounted on glass stirring rods, and the ends coated with "Tufnol" lacquer. Before use, they were etched for 10 sec. in 5N-hydrochloric acid to remove the worked surface. Care was taken to ensure that the two cylinders were rotated at the same

* Part II, *J.*, 1951, 1490.

point in the reaction vessel. Between runs they were stored under 0·003N-sulphuric acid. The observed values of k_1 are recorded in Table 2. In Fig. 1, values of the function $(\Sigma v \,.\, \Delta \log c)/A$ (see Part I) are shown plotted against time for one run with each cylinder. The origin for one run is displaced to distinguish the experimental points; the standard slope for zinc foil is included for comparison.

TABLE 2.

Orientation of *c*-axes	k_1 (obs.)	Mean k_1	Orientation of *c*-axes	k_1 (obs.)	Mean k_1
Horizontal	0·114, 0·113	0·114	Vertical	0·112, 0·109	0·111

Rate of Stirring.—The effect of varying the rate of rotation of the specimen was investigated over the range 50—200 r.p.m. In each case, the rate of stirring was maintained constant to

FIG. 1.

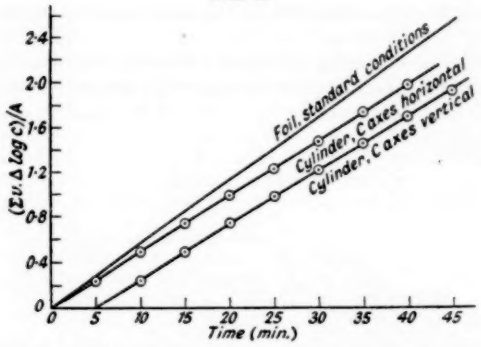
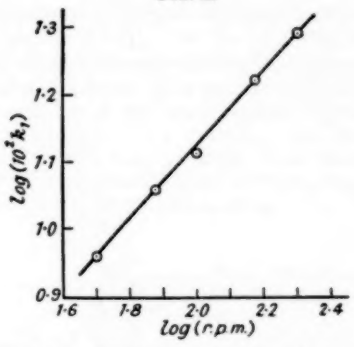


FIG. 2.



within ±1% by means of the stroboscope and manual control described in Part I. The observed values of k_1 are recorded in Table 3. The log–log plot of the mean values of k_1 against rate of stirring is shown in Fig. 2.

TABLE 3.

Rate of stirring, r.p.m.	50	75	100	150	200
k_1 (obs.)	0·0919, 0·0910	0·114, 0·113	0·130, 0·130	0·167, 0·166	0·198, 0·194
Mean k_1	0·0915	0·114	0·130	0·167	0·196

Rate on the Leading and the Trailing Edges.—Examination of the specimen after a run frequently revealed a difference in the extent of attack on the leading and the trailing edges. This effect was particularly noticeable in the runs in very dilute iodine solutions reported in Part I, large patches of the original polished surface being left on the trailing edges. To investigate the effect, one half of each side of a standard size specimen was coated with " Tufnol " lacquer so that by placing it in the specimen holder one way up the two leading edges were exposed, whereas by placing it in the holder the other way up the two trailing edges were exposed to attack. Preliminary tests confirmed that the coating was resistant to attack and penetration by iodine. The observed values of k_1 are recorded in Table 4. The results for one run in which the leading edges and for one in which the trailing edges of the same specimen were exposed are shown in Fig. 3.

TABLE 4.

	Specimen no. 1	Specimen no. 2
Leading edge attack : k_1	0·135	0·135
Trailing edge attack : k_1	0·125	0·127
Mean k_1	0·130	0·131

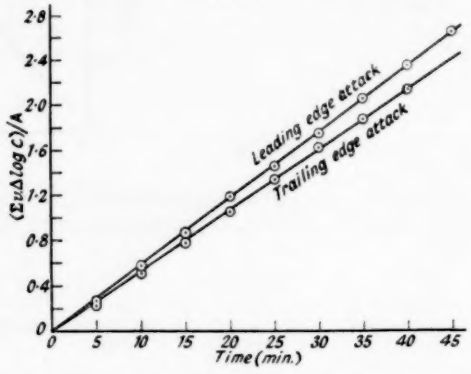
DISCUSSION

The fact that, under the same conditions, copper, amalgamated copper, brass, lead, nickel, and zinc dissolve at the same rate within the limits of experimental error confirms the work of Van Name and his co-workers (*Amer. J. Sci.*, 1910, **29**, 237; 1911, **32**, 207), and suggests that the observed rate is determined solely by the rate of transport of iodine to the metal surface. If, then, the rate of chemical reaction at the surface is too fast to

influence the observed rate, the latter should be independent of the crystal face exposed to attack. No reaction for which the observed rate varies on different faces of a zinc crystal has been reported in the literature, but for other systems the difference is quite marked; *e.g.*, Spring (*Z. physikal. Chem.*, 1888, **2**, 13) found the rate of dissolution in dilute acids of Iceland spar at surfaces cut parallel to the crystal axis to be *ca.* 1·3 times larger than at surfaces cut parallel to the natural plane of cleavage. As is well known, measurements of physical properties of zinc crystals show similar variations. Thus, Bochvar and Sviderskaya (*Chem. Abs.*, 1946, **40**, 2369) report that the coefficient of linear expansion along the main axis of the hexagonal prism is 3·7 times larger than the corresponding value measured normal to this axis; McLennan, Ruedy, and Cohen (*Proc. Roy. Soc.*, 1928, *A*, **121**, 9) find the corresponding ratio of the magnetic susceptibilities to be 1·6. The observed ratio, 1·03, for the rate of dissolution of the two zinc cylinders would therefore suggest that the observed rate is the same in each case, within the experimental limits of error.

On the assumption of transport control, the remaining results are readily interpreted. The dependence of k_1 on the rate of stirring is a characteristic feature of such reactions; as will be seen from Fig. 2, the dependence may be expressed $k_1 = 0{\cdot}0103$ (r.p.m.)$^{0{\cdot}56}$, the

FIG. 3.



power being in reasonable agreement with the square-root relationship deduced by Levich (*Acta Physicochim. U.R.S.S.*, 1942, **17**, 257). From the results the variation of δ, the thickness of the Nernst diffusion layer (*Z. physikal. Chem.*, 1904, **47**, 52), with rate of stirring can be calculated. On the simple Nernst theory $\delta = D/k_1$, where D is the coefficient of diffusion of iodine. Values calculated from this expression, by using the value $D = 1{\cdot}22 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ obtained from the empirical relation derived in Part II (*loc. cit.*), are recorded in Table 5. Also shown are the values calculated from Levich's expression $\delta = 1{\cdot}613 D^{\frac{1}{3}} \nu^{\frac{1}{6}} \omega^{-\frac{1}{2}}$, where ω is the angular velocity of the specimen, and ν the kinematic viscosity of the solution. [*Note.* Levich (*loc. cit.*) obtained the value 1·62 for the constant of proportionality, but this is based on too small a value of the function Γ (4/3) coupled with a slight arithmetical error.]

TABLE 5.

ω, rad. sec.$^{-1}$	5·23	7·85	10·5	15·7	20·9
$10^3\,\delta$ (calc. from Nernst eqn.), cm.	7·98	6·40	5·61	4·37	3·72
$10^3\,\delta$ (calc. from Levich eqn.), cm.	7·36	6·01	5·20	4·25	3·68

The agreement is satisfactory, particularly at the higher rates of stirring, as required by Levich's treatment. Although this author derived the expression for the particular case of a plane disc electrode rotating about an axis perpendicular to the plane, he observes that it should be of wider application. The independent nature of this check is of importance since, for the plane disc electrode and for the present system, it now seems possible to calculate the thickness of the conventional diffusion layer without reference

to the experimentally observed rate. However, these values are to be regarded as expressing the mean thickness of the layer rather than the actual thickness at any given point on the surface, since the results reported in Table 4 show that the rate is some 7% higher on the leading edges of the specimen than on the trailing edges. This difference is almost certainly due to slight turbulence of the fluid flow, as is shown by the fact that the value of the " stirring coefficient," 0·56, is slightly higher than the value of 0·5 derived by Levich for non-turbulent flow. This point is considered further in the following paper.

Comparison of the rate of dissolution of copper in the presence of a film of cuprous iodide ($k_1 = 0{\cdot}114$) with the standard rate of dissolution of zinc ($k_1 = 0{\cdot}130$), together with the fact that for copper the rate falls off with time, suggests that the film offers resistance to the transfer of iodine to the surface. This is in agreement with the observed fall-off in the rate of dissolution of lead in the presence of a film of lead iodide, and for zinc in the absence of acid, *i.e.*, in the presence of a film of hydroxide (Fig. 4, Part I). Similar results have been reported by Van Name and Edgar (*loc. cit.*, 1910). On the other hand, Bircumshaw and Everdell (*J.*, 1942, 598) found that slowly deposited films of cuprous iodide offer no resistance to mass transfer in aqueous systems.

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127. *The Kinetics of the Dissolution of Zinc in Aqueous Iodine Solutions. Part IV.**

By A. C. Riddiford and L. L. Bircumshaw.

The results reported in previous papers may be correlated by means of the expression $Nu = 0{\cdot}558Re^{0{\cdot}56}P_r^{0{\cdot}27}$, in agreement with the theory developed by Levich. The fluid flow is but slightly turbulent. The reaction may be used to characterise the fluid flow in other solid–liquid systems. The validity of Buben and Frank-Kamentzkiĭ's treatment is discussed.

From the work reported in Parts I—III (*J.*, 1951, 598, 1490, and preceding paper) it is concluded that the observed rate of dissolution of zinc in aqueous solutions of iodine is determined solely by the rate of transport of iodine to the metal surface. This system, therefore, is suitable for the characterisation of the fluid flow in other solid–liquid systems. In this connection, it seems desirable to see how far the results obtained for the present system may be correlated by dimensional analysis (see Agar, *Faraday Soc. Discuss.*, 1947, **1**, 26).

The surface of the specimen may be regarded as the only boundary surface of the system. This is justified on the following grounds. First, an increase in the initial volume of solution has but a small effect on the observed value of k_1, the rate constant per unit area at unit volume, as will be seen from Table 1. Duplicate runs were performed

Table 1.

Initial vol. of soln., ml.	300	350	400
Mean k_1 (obs.) †	0·130	0·130	0·134

† Throughout this paper, k_1 is given in the units cm. min.$^{-1}$, except in Table 2.

in a second reaction vessel [Fig. 1(*a*), Part I], the initial volume of solution being 350 ml. The observed values of k_1 (0·133, 0·133) are closely similar to the values recorded in Table 1,

* Part III, preceding paper.

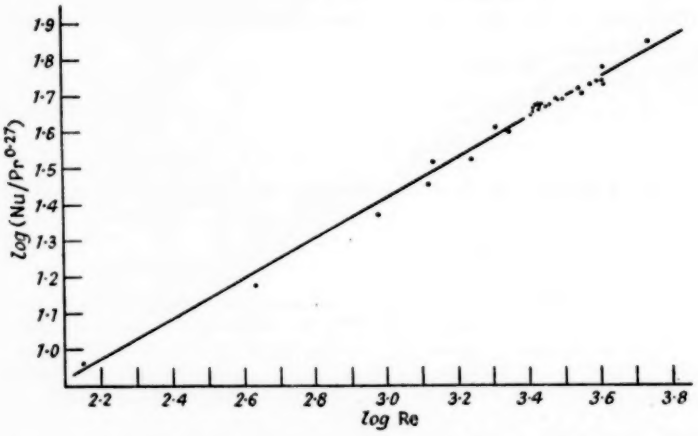
the inference being that the containing walls are too far from the specimen to affect the observed rate. Moreover, the theory developed by Levich (*Acta Physicochim., U.R.S.S.*, 1942, **17**, 257) and utilised in the preceding paper requires that the only surface of discontinuity in the system be that of the solid–liquid interface. The measure of agreement found between values of δ, the thickness of the "diffusion layer," calculated from Levich's theory and from the simple Nernst theory suggests that for the present system the assumption is justified.

In these circumstances, the problem reduces to the determination of the relation between k_1, the characteristic velocity of the system U, the characteristic length l, the coefficient of diffusion of iodine D, the kinematic viscosity of the solution ν, and the mean height of the surface irregularities h. The relation between these six quantities may be expressed as a relationship between four dimensionless groups as follows:

$$\left(\frac{k_1 l}{D}\right) = A'\left(\frac{Ul}{\nu}\right)^a\left(\frac{\nu}{D}\right)^b\left(\frac{h}{l}\right)^c$$

where the ratio $k_1 l/D$ is termed Nusselt's number Nu; Ul/ν, Reynold's number Re; ν/D, Prandtl's number Pr; and h/l is the relative roughness of the surface. A' is a number

FIG. 1.



dependent only on the shape of the specimen and the type of fluid flow. As discussed in Part I, Nikuradse (*Forschungsheft* No. 361, Suppl. to *Forschung auf dem Gebiete des Ingenieurwesens*, 1933, 4*B*, July/August) has shown that relative roughness over the range 1/507 to 1/15 is without effect on the friction factor in the region of non-turbulent flow, but that it has considerable effect in the case of turbulent flow. This effect becomes important at an Re which is smaller the larger the value of the relative roughness. Since the values of h/l for the present system are small and, as will be shown shortly, the flow was but slightly turbulent, the index c on the relative roughness may be set equal to zero.

The characteristic velocity of the system is taken to be the linear velocity of the edge of the specimen and l to be one half the width of the specimen, $L/2$, whence $Re = (\pi L^2 n)/2\nu$, where n is the number of revolutions of the specimen per sec. Then since, as shown in Parts II and III, k_1 is proportional to $n^{0.56}$ and to $\nu^{-0.76}$, whilst $D = 0{\cdot}0529(1/\nu)^{0.63}$, the Reynold's power $a = 0{\cdot}56$ and the Prandtl power $b = 0{\cdot}27$. Finally, the value of the number A' may be calculated from the experimental results. Values so calculated are shown in the last column of Table 2, in which are tabulated values of k_1, ν, U, D, Nu, Re, and Pr. Under the heading "System" references to the experimental sections are given, thus II. 1 denotes Part II, Table 1, etc. As will be seen, the calculated value of A' is constant and has a mean value of 0·558. The maximum deviation from the

mean value is 8·2%, the average deviation being 3·4%. This is considered satisfactory in view of the fact that *Re* has been varied over a 38-fold range, whilst the variation in *Pr* is 238-fold. Hence, for the present system, $Nu = 0{\cdot}558 \,.\, Re^{0{\cdot}56} \,.\, Pr^{0{\cdot}27}$. In Fig. 1 log $(Nu/Pr^{0{\cdot}27})$ is shown plotted against log *Re*, the solid line representing the above expression. In view of the somewhat uncertain diffusion data, the correlation is satisfactory.

TABLE 2.

System	10^3k_1, cm. sec.$^{-1}$	$10^3\nu$, cm.^{2} sec.$^{-1}$	U, cm. sec.$^{-1}$	10^5D, cm.^{2} sec.$^{-1}$	*Nu*	*Re*	*Pr*	*A'*
II. 1	2·18	0·870	15·7	1·22	269	2710	716	0·577
,,	2·22	0·819	,,	1·27	263	2880	648	0·560
,,	2·32	0·751	,,	1·33	261	3140	564	0·549
,,	2·48	0·659	,,	1·45	257	3580	455	0·533
,,	2·65	0·628	,,	1·49	266	3750	421	0·548
,,	2·73	0·600	,,	1·53	267	3930	391	0·547
,,	2·73	0·581	,,	1·57	262	4050	371	0·534
,,	2·72	0·577	,,	1·57	259	4080	367	0·528
II. 2	1·78	1·065	,,	1·07	249	2210	993	0·549
,,	1·43	1·350	,,	0·923	232	1750	1 460	0·525
,,	1·15	1·782	,,	0·774	222	1320	2 300	0·520
,,	0·878	2·479	,,	0·629	210	950	3 940	0·512
,,	0·483	5·490	,,	0·381	190	429	14 400	0·513
,,	0·237	16·58	,,	0·190	187	142	87 300	0·580
II. 3	2·17	0·889	,,	1·20	271	2650	742	0·584
,,	2·18	0·833	,,	1·25	262	2830	666	0·559
,,	2·32	0·786	,,	1·30	268	3000	605	0·568
,,	2·18	0·876	,,	1·21	271	2690	724	0·580
,,	2·32	0·769	,,	1·32	264	3060	584	0·558
,,	2·55	0·677	,,	1·42	269	3480	476	0·560
,,	2·12	0·904	,,	1·19	268	2610	762	0·576
,,	2·07	0·905	,,	1·19	261	2600	763	0·563
,,	2·02	0·917	,,	1·18	257	2570	780	0·555
,,	2·12	0·877	,,	1·21	263	2690	725	0·564
III. 3	1·53	0·870	7·85	1·22	188	1350	716	0·593
,,	1·90	0·870	11·8	1·22	234	2030	716	0·589
,,	2·17	0·870	15·7	1·22	267	2710	716	0·572
,,	2·78	0·870	23·6	1·22	343	4060	716	0·588
,,	3·27	0·870	31·4	1·22	403	5420	716	0·587

According to Levich (*loc. cit.*) the equations for the rotating disc system are of the form :

$$\text{Non-turbulent flow}: Nu = A' \,.\, Re^{0{\cdot}5} \,.\, Pr^{0{\cdot}33}$$
$$\text{Turbulent flow}: Nu = B \,.\, Re^{a} \,.\, Pr^{0{\cdot}33}$$

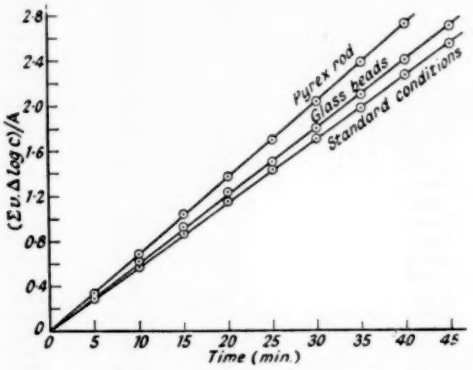
i.e., the dependence of *Nu* on *Pr* is the same for both types of flow. The change in flow-type is accompanied by a change in the " apparatus number," and in the dependence of *Nu* on *Re*. As the degree of turbulence increases, *a* increases from 0·5 to a limiting value of unity. That in fact there is a lower critical Reynold's number for stirred systems, analogous to the system of pipe-flow, has been shown by Hixson and Luedeke (*Ind. Eng. Chem.*, 1937, **29**, 927) and by Hixson and Baum (*ibid.*, 1941, **33**, 478; 1942, **34**, 194). The present results are in reasonable agreement with Levich's theory, the power of *Re* indicating that the flow was but slightly turbulent.

This was confirmed experimentally by rotating a specimen in 300 ml. of water and inserting permanganate solution from a fine capillary tube. At all rates of stirring used in the present investigation, filaments originating along the height of the specimen flowed in circular paths about the axis of rotation. Moreover, the degree of turbulence in the system could readily be increased. Pyrex rod, 1 cm. in diameter, was drawn into 4-cm. lengths with pointed ends. A number of these, of total volume 50 ml., were packed into the bottom of the reaction vessel. In the lower layer, the lengths were packed vertically; the few remaining lengths were placed on top to form a second layer. Fig. 2 shows values of the function $(\Sigma v \,.\, \Delta \log c)/A$ (see Part I) plotted against time for one run; also shown is the plot for a run using glass beads, 0·4 cm. in diameter, of total volume 50 ml. The effect is large, and surprisingly reproducible. Thus, for runs using the Pyrex rod were found values of $k_1 = 0{\cdot}157, 0{\cdot}155, 0{\cdot}157, 0{\cdot}158$.

From the simple Nernst theory, k_1 should be directly proportional to D (*i.e.*, Nu should be constant), provided the rate of stirring is constant. Examination of the relevant values recorded in Table 2 shows that Nu is in fact approximately constant except for the cases where very viscous solutions were used. It is a feature of the study of transport-controlled reactions that it is necessary to vary the experimental conditions over very wide ranges in order to be able to check the validity of any conclusion.

Lastly, mention should be made of Buben and Frank-Kamenetzkiĭ's extension (*J. Phys. Chem. U.S.S.R.*, 1946, **20**, 225) of the dimensional treatment to systems in which the flow is strongly turbulent. These authors postulate that for the limiting case of pure turbulence k_1 must be independent of both D and ν, *i.e.*, k_1 is entirely determined by the

FIG. 2.



rate of flow. To express this condition they write $k_1 = MU$, where M is termed Margulis's number. As the limiting case of complete turbulence of flow is approached, M must tend to a constant value. Since this limiting case is not attainable in practice, M will always depend in some way on Re and Pr, this dependence being smaller the greater the degree of turbulence. They show that, under conditions of strong turbulence of flow, M is of the same order of magnitude (*ca.* 5×10^{-5}) for the dissolution of several solids in aqueous solutions at room temperature. However, for the more viscous solutions used in the present investigation, M is of the same order of magnitude under flow conditions far removed from strong turbulence. One must conclude that there is some doubt as to the validity of their extension as it stands at present.

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128. *Enzymic Synthesis and Degradation of Starch. Part XV.* β-Amylase and the Constitution of Amylose.*

By Stanley Peat, S. J. Pirt, and W. J. Whelan.

The action of Balls's crystalline β-amylase is shown to be different from that of amorphous preparations of β-amylase inasmuch as it converts potato amylose to the extent of only 70% into maltose. Evidence is presented that a standard preparation of β-amylase from soya beans contains, in addition to true β-amylase, an enzyme (Z-enzyme) which supplements the β-amylase in effecting the complete conversion of amylose into maltose. It appears that some degree of branching occurs in potato amylose and that this branching impedes the progress of β-amylolysis. The branch links of amylose are different from the α-1 : 6-links of amylopectin and are specifically attacked by Z-enzyme which is without action on the amylopectin branch links. At pH 3·6 the action of Z-enzyme is inhibited.

The literature relating to the β-amylolysis of whole starch reveals differences of opinion as to the true limit of conversion into maltose. Thus, Hopkins, Murray, and Lockwood (*Biochem. J.*, 1946, **40**, 507) state that the arrest point for starch is 56%, whereas Myrbäck (*Adv. Carbohydrate Chem.*, 1948, **3**, 265) gives the figure of 61%. We now report a study of the action of the crystalline β-amylase of sweet-potato and of soya-bean β-amylase on starch and its components, and offer a partial explanation of the previous inconsistencies. A preliminary account of this work has been published in *Nature*, 1949, **164**, 499.

Our specimen of the crystalline β-amylase of sweet potato was the generous gift of Dr. A. K. Balls and an account of its preparation and properties is given by Balls, Walden, and Thompson (*J. Biol. Chem.*, 1948, **173**, 9).

β-Amylase is generally supposed to convert amylose completely into maltose, although conversions which are quantitatively complete have seldom been reported. In the apparent completeness of this hydrolysis lies the strongest evidence for the view that amylose possesses a linear structure, free from branch linkages such as those which impede the hydrolysis of amylopectin by β-amylase. When, however, crystalline sweet potato β-amylase was allowed to act on amylose at pH 4·8 its rapid action ceased abruptly at 70% conversion into maltose (Fig. 1). Thereafter an exceedingly slow further action was observed, the rate of which was about 0·02% of the initial rate. Measurements at successive stages showed that the enzyme lost little of its activity during the incubation (Table 3, p. 710). There remained a polysaccharide which stained blue with iodine, exhibiting peak absorption at the same wave-length as the original amylose, *i.e.*, at 640—650 mμ. Possible causes of this incomplete conversion of amylose into maltose were investigated in turn. The possibilities that maltose, a product of the reaction, inhibited further enzyme action or that the enzyme established an equilibrium between amylose and maltose were discounted by methods described in the Experimental section (cf. Table 7, p. 711).

Another possibility was that part of the amylose was protected from enzyme action by the physical change which, following K. H. Meyer *et al.* (*J. Phys. Chem.*, 1949, **53**, 319), we will describe as " ageing." Ageing may well be the initial stage in a process of aggregation which ultimately results in the amylose becoming insoluble (retrogradation), but it is important to note that " ageing " and " precipitation " are not synonymous terms. Experiments were next designed to test the possibility that the ageing of amylose was responsible for the incompleteness of β-amylolysis with the crystalline enzyme.

(1) An amylose solution was stored for 15 days at pH 6·5 and 35·4° and portions were removed at intervals for the determination of the limit of hydrolysis by crystalline β-amylase at pH 4·8. The % conversion into maltose at the arrest point shifted upwards from 67·0 to 71·5 (Table 8, p. 712); ageing of the amylose solution would have been expected to increase the resistance to β-amylase not to decrease it.

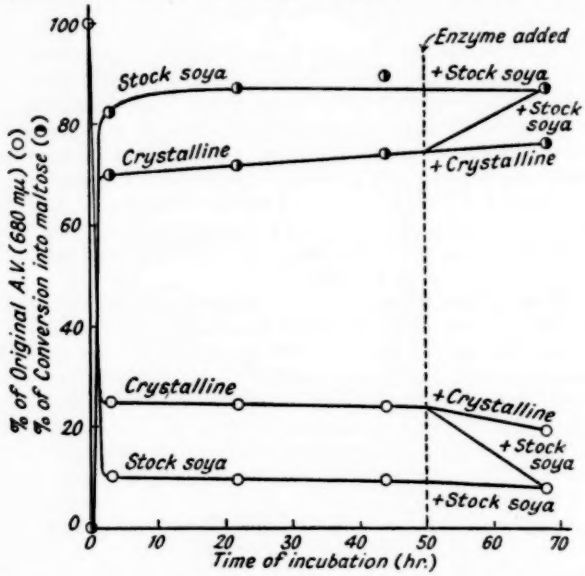
* Part XIV, *J.*, 1951, 1451.

(2) The ageing process can be reversed by treatment of an amylose solution with alkali. Amylose was therefore incubated with crystalline β-amylase at pH 4·8 until the arrest point was reached. A portion of the solution was then made alkaline (pH >12) and heated at 100° for one minute and, after adjustment of the pH to 4·8, fresh enzyme was added. The further slow action of the enzyme on the "rejuvenated" polysaccharide was indistinguishable from its action on the untreated residual polysaccharide (Table 9, p. 712).

Alternatively, Bernfeld and Gürtler (*Helv. Chim. Acta*, 1948, **31**, 106) eliminate the effects of ageing in digests by the device of a slow addition of the amylose in alkaline solution to the buffered enzyme. With a standard preparation of wheat β-amylase they observed a conversion of 100% under these conditions. When, however, we used this technique with crystalline β-amylase, the limit of conversion of the amylose remained at 72·3% (Table 10, p. 712).

(3) Meyer and Gonon (*ibid.*, 1951, **34**, 294) have shown that an increase in the amylase concentration minimises the effect of ageing. Nevertheless, we found that a nine-fold

FIG. 1. *Action of crystalline β-amylase and stock soya-bean β-amylase on amylose* (B.V. 1·24) *at* pH 4·8.



increase in the usual concentration of crystalline β-amylase did not materially influence the observed arrest point (Table 11, p. 712).

(4) The degree of ageing of an amylose sample is closely connected with the method of its preparation and storage, but it is found that the % conversion into maltose by the same sample of β-amylase does not vary from one amylose preparation to another (Part XIII, *J.*, 1951, 801) and, moreover, amyloses from different plant sources are converted to the same degree (*ca.* 70%) by a pure β-amylase (Part XVI, succeeding paper). Clearly the incompleteness of the hydrolysis of amylose by crystalline β-amylase cannot be associated with any of the recognised attributes of ageing.

(5) Finally, if the ageing of amylose were responsible for the resistance to β-amylolysis, then the addition of stock soya-bean β-amylase to an amylose already hydrolysed to the limit by crystalline β-amylase would not be expected to induce further hydrolysis. Such an addition did, however, cause the limiting conversion to increase rapidly from 70 to 86% (Fig. 1), the latter value being the normal limit of conversion of this amylose by the stock soya preparation.

We are left with the proposition that the incompleteness of the conversion by the

crystalline enzyme is due to the occurrence in amylose of structural anomalies which impede the progressive action of β-amylase along the amylose chains. In amylopectin, these " anomalies " are the branch linkages and it is reasonable to suppose that in amylose also they are glucosidic linkages different from the α-1 : 4-chain links. That these anomalous links have previously escaped detection would appear to be due to the presence in the usual β-amylase preparations of another enzyme which either hydrolyses the anomalous linkages or, like α-amylase, by-passes them and cleaves the " inner " chain-links, thereby exposing new non-reducing end groups to β-amylolytic action. A decision between these alternatives was made by a comparison of the actions of crystalline β-amylase and of a stock preparation from soya bean on amylopectin.

With potato amylopectin as substrate and at a pH of 4·8 the crystalline and stock soya-bean enzymes behaved identically; the same arrest point was observed, at 52% conversion into maltose (Table 6, p. 711). If the soya-bean preparation had contained an α-amylase capable at pH 4·8 of splitting the inner chains of amylopectin, the limiting amylolysis brought about by this preparation would have been greater than that achieved by crystalline β-amylase. The crystalline β-amylase shows the same well-defined arrest point also at pH 6·5 and 3·6 and moreover this limit of conversion is not further increased by the addition of fresh enzyme (Table 12, p. 713). On the other hand, the soya-bean preparation appears not to be quite free from α-amylase, the action of which on amylopectin becomes manifest at pH 6·5 (Table 6, p. 711), although as already stated, such action is entirely suppressed at pH 4·8.

These results with amylopectin having demonstrated that the action of the soya-bean preparation on amylose at pH 4·8 cannot be ascribed to the presence in it of α-amylase, the conclusions must be drawn (*a*) that amylose possesses a branched structure and that the branch links, although different from those in amylopectin, obstruct the action of β-amylase in the same manner and (*b*) that β-amylase as normally isolated from soya bean contains a factor capable of removing these anomalous links.

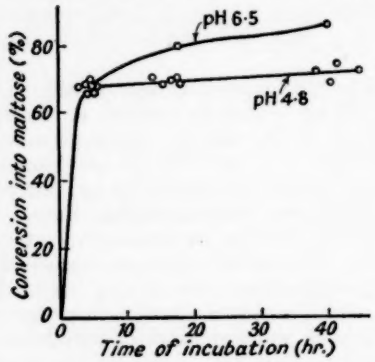
That this new factor is an enzyme was demonstrated in two ways First, its activity with respect to amylose varies with the hydrogen-ion concentration. At pH 3·6 the soya-bean preparation and the crystalline β-amylase behave identically inasmuch as hydrolysis of amylose ceases abruptly at 70% conversion in each case (Table 4, p. 710). These results suggest that the factor in the bean preparation which supplements β-amylolysis of amylose at pH 4·8 (see Fig. 1) is inactive at pH 3·6. Secondly, the factor is thermolabile. When an aqueous solution of the stock soya-bean preparation was heated at 63° for varying times and then allowed to hydrolyse amylose at pH 4·8 it was found that the degree of conversion varied inversely with the period of heating (Table 13, p. 713). Soya-bean β-amylase which had been held at 63° for 45 minutes converted only 72·5% of the amylose into maltose during 17 hours' incubation. The assumption that the factor is an enzyme is therefore justified and it will be referred to hereafter as Z-enzyme. Final proof of its enzymic nature has been obtained by its isolation from soya beans in a form which is free from α- or β-amylases and can function independently of β-amylase (Thomas, Whelan, and Peat, *Biochem. J.*, 1950, **47**, xl; Part XVII of this series).

When amylose was the substrate for crystalline β-amylase in solutions buffered to pH 3·6, 4·8, and 6·5, a clearly defined arrest point occurred in each case at a value between 67·5 and 70% conversion into maltose. Fig. 2 records the combined results of six experiments carried out at pH 4·8 and indicates the good reproducibility of the results; Table 4 (p. 710) shows that the same behaviour was apparent at pH 3·6. The rate of the end-point " drift " occurring at pH values of 3·6 and 4·8 is insignificant when compared with the rate of the initial hydrolysis. The magnitude of the " drift " at pH 6·5 is, however, more appreciable (Fig. 2) and it is suggested that this may be due to a trace of Z-enzyme in the crystalline preparation. Since the pH optimum for Z-enzyme action is 6·1 (See Part XVII) it might be expected to exert a greater effect at pH 6·5 than at pH 4·8. The results in Table 11 (p. 712) show that the renewal of enzyme in high concentration after the arrest point of β-amylase action on amylose at pH 4·8 had been attained caused some additional hydrolysis of the amylose limit β-dextrin. This did not happen at pH 3·6 (Table 4, p. 710) It appears therefore that the crystalline β-amylase, although free from α-amylase

(incidentally, we have shown it to be free also from maltase), was contaminated with a trace of Z-enzyme, the action of which became evident at pH 6·5 but not at pH 3·6 or 4·8. An attempt preferentially to destroy the impurity in the crystalline enzyme by the heat treatment described above was not successful (Table 14, p. 713), but it should be pointed out that whereas Z-enzyme could be heat-inactivated in the early stages of purification of β-amylase (Part XVI, succeeding paper), it could not be removed by this method when it was present in a more highly purified β-amylase preparation.

A cognate experiment was carried out by Potter, Hassid, and Joslyn (*J. Amer. Chem. Soc.*, 1949, **71**, 4075) who incubated amylose (from apple starch) with a high concentration of crystalline β-amylase at pH 4·7. The quantity of enzyme used is equal to 50 000 units on our scale and was, further, renewed after 24 hours. The reducing power was not measured until after further incubation for 24 hours and a conversion limit of 90%, as opposed to our 70%, was recorded. Since the amount of β-amylase added was sufficient to hydrolyse the amylose within a few minutes, it is not improbable that even a minute proportion of impurity (Z-enzyme) could considerably enhance the degree of hydrolysis at these concentrations. Experiments with unfractionated apple starch (G. J. Thomas, unpublished

FIG. 2. *Action of crystalline β-amylase on amylose* (B.V. 1·47) *at* pH 4·8 *and* pH 6·5.



results) indicate that Z-labile linkages are, in fact, present; the limiting conversions into maltose by β-amylase and β-amylase + Z-enzyme at pH 4·8 are, respectively, 54 and 60%, values which correspond closely to those obtained with whole potato starch (Table 1). Furthermore amylose preparations from three other plants all show the same definite arrest point as potato amylose when acted upon by pure β-amylase (see Part XVI).

TABLE 1. *Comparison of the actions of crystalline and stock soya-bean β-amylases on starch polysaccharides at different* pH *values.*

		Amylose (B.V. 1·47)		Potato starch (B.V. 0·470)		Amylopectin (B.V. 0·193)	
		% Convn.† at arrest point	A.V. (680 mμ) at arrest point	% Convn. at arrest point	A.V. (680 mμ) at arrest point	% Convn. at arrest point	A.V. (680 mμ) at arrest point
Enzyme	pH						
Crystalline	3·6	70·7	0·287 *	52·2	0·194	51·8	0·108
Stock soya	,,	69·7	0·293 *	52·3	0·205	51·8	0·103
Crystalline	4·8	67·5	0·411	53·2	0·208	52·1	0·110
Stock soya	,,	96·8	0·056	60·5	0·118	53·0	0·111
Crystalline	6·5	67·5	0·410	53·8	0·200	52·0	0·110
Stock soya	,,	93·0	0·057	—	—	>63·0 ‡	<0·09 ‡

* Amylose (B.V. 1·24). † % Convn. = % Conversion into maltose. ‡ See Table 6.

Table 1 summarises the results with respect to the action of β-amylase on potato starch and on its separated components. The values given for % conversion and A.V. (680 mμ) at the arrest points are averages of a number of experimental results.

Calculations made from the data in Table 1 indicate that whole starch may not be a

simple mixture of the amylose and the amylopectin obtained from it by the usual technique (Part XIII, *J.*, 1951, 801). In Table 2, the observed values for potato starch are contrasted with the values calculated for artificial mixtures of amylose and amylopectin in the stated proportions.

TABLE 2. *Action of β-amylase on whole potato starch.*

		Crystalline β-amylase		Stock soya-bean β-amylase	
	B.V.	% Convn.	A.V. (680 mμ)	% Convn.	A.V. (680 mμ)
Observed values † for whole starch	0·470	53·2	0·208	60·5	0·118
Calculated values for mixtures :					
Am/Ap * = 23/77	0·486	55·6	0·179	63·0	0·098
= 20/80	0·448	55·2	0·170	62·6	0·100
= 25/75	0·513	56·0	0·183	63·9	0·097

* Am/Ap = ratio of amylose to amylopectin by weight. † See Table 5.

It is clear from Table 2, that if the amylose and amylopectin used are mutually uncontaminated then the composition of starch cannot be accurately expressed in terms of two components alone (for evidence of the purity of these components see Part XIII, *J.*, 1951, 801). These results are explicable on the view that there is present in whole starch a third component which has a slightly higher blue value and a lower limit of β-amylolysis than has amylopectin. One is reminded here of the polysaccharides of structure intermediate between amylose and amylopectin, which are synthesised by mixtures of phosphorylase and Q-enzyme (Parts VIII and IX, *J.*, 1950, 3022, 3027). Lansky, Kooi, and Schoch (*J. Amer. Chem. Soc.*, 1949, **71**, 4066) have also advanced evidence for the existence in starch of from 5 to 7% of a polyglucose which is intermediate in structure between the linear and branched components.

In the succeeding communications reports are given of the properties of purified soya-bean β-amylase (the behaviour of which is identical with that of crystalline β-amylase) and also of the properties and function of Z-enzyme. Although we have provided evidence that ageing of amylose is not primarily responsible for the incompleteness (70%) of the conversion of amylose into maltose by pure β-amylase, we have been careful to employ conditions of β-amylase action under which ageing does not normally occur. We have found that amylose can be caused to age under appropriate conditions which will be defined in a later paper, and that when this happens the limit of conversion by pure β-amylase may be as low as 40%. This change is reversed by alkali treatment, the conversion then returning to the normal limit of not more than 70%. Two effects may therefore be responsible for the incompleteness of the hydrolysis of amylose by β-amylase, first, the existence in amylose of anomalous linkages, and secondly, the apparently physical change in the amylose described as ageing.

EXPERIMENTAL

Analytical Methods.—For the methods used in determination of iodine stains of polysaccharides see Bourne, Haworth, Macey, and Peat (*J.*, 1945, 924). The standard method of blue-value determination was occasionally modified by using an amylose solution containing acetate buffer (pH 4·8). Under these conditions the blue values of the purest amyloses (B.V. >1·40) were depressed by 0·05, those of less pure amyloses, *e.g.*, B.V. 1·24, were unaffected. Reducing sugar was determined by use of the Somogyi copper reagent (*J. Biol. Chem.*, 1945, **160**, 61) as in Pirt and Whelan's work (*J. Sci. Food Agric.*, 1951, **2**, 224, where the method of acid hydrolysis, which was also used in the analysis of starch polysaccharides, is described). α-Amylase activity was determined as in Part X (*J.*, 1950, 3566). In determinations of the activity of the enzyme at intervals during the β-amylolysis of a polysaccharide (Table 3) the scale of the experiment was reduced to one-tenth of that given in Part X (*J.*, 1950, 3566).

Preparation of Starch Fractions.—The amylose of B.V. 1·24 was prepared by the method of Bourne, Donnison, Peat, and Whelan (*J.*, 1949, 1). All other fractions were prepared as in Part XIII (*J.*, 1951, 801).

Preparation of Enzymes.—Stock soya-bean β-amylase, which contains Z-enzyme, was prepared as in Part II (*J.*, 1945, 882). Crystalline sweet potato β-amylase was prepared by Balls,

Walden, and Thompson (*loc. cit.*) and we express our thanks to Dr. A. K. Balls for the gift of the samples used in this work.

β-*Amylolysis of Starch Polysaccharides.*—(a) ***Preparation of digests.*** All digests contained the following constituents in the same relative amounts : polysaccharide (*ca.* 30 mg.), benzene (0·25 ml.), 0·25N-sodium hydroxide (10 ml.), phenolphthalein indicator (0·01%; 0·05 ml.), N-hydrochloric acid (to neutralise the alkali), 0·2M-acetate buffer (6 ml.) or 0·053M-citrate buffer (12 ml.), β-amylase solution (0·5 ml. containing 1300 units of enzyme), and water to 50·5 ml. The digest was covered with a layer of toluene.

The dried polysaccharide was introduced into a dry 50-ml. flask and wetted with benzene, and sodium hydroxide solution was added. After shaking, dissolution was completed by heating the flask on a boiling water-bath for 3 minutes. The solution was cooled, indicator added, and the whole neutralised. Buffer solution and water were then added almost to the graduation mark. The flask was placed in the thermostat and allowed to attain the temperature of incubation (35·4°). After dilution of the solution to the mark the enzyme solution (see below) was added. Aliquot portions were removed at intervals for the determination of A.V. (680 mμ), maltose, and residual β-amylase activity. At the same time a control digest, used to determine the reducing power of the enzyme, was incubated. This digest contained all the above constituents except the polysaccharide. The control showed that only the stock soya-bean preparation possessed any reducing power. As a precaution against contamination by salivary amylase, the mouthpieces of all pipettes required for the digests were plugged with cotton wool.

(b) *Preparation of enzyme solutions.* When stock soya-bean β-amylase was used the enzyme powder was weighed into a centrifuge tube, and water (equal to half the required final volume) was added. The suspension was triturated with a glass rod and after 4—5 minutes an equal volume of the buffer solution used in the digest was added. The solutions were mixed and the sediment was removed on the centrifuge. This procedure eliminated the precipitate which formed when the enzyme preparation was buffered to an acid pH. The final enzyme concentrations of these stock solutions were 2600 units/ml. An unbuffered aqueous solution of the crystalline β-amylase was used, its concentration again being adjusted to 2600 units/ml.

(c) *Maltase activity of the enzymes.* Tests for maltase activity were made by incubating a digest as above but replacing the polysaccharide by maltose (25 mg.). Crystalline β-amylase had no action on maltose during 200 hours at pH 3·6, 4·8, 5·6, or 6·5. The specimen of stock soya-bean β-amylase used most frequently in this work did, however, cause an increase in reducing power of 2% in 87 hours at pH 4·8. Where necessary, the reducing power of a polysaccharide–β-amylase digest was corrected for this maltase activity. Tables 3—6 are self-explanatory.

Successive Actions of Crystalline and Stock Soya-bean β-Amylases on Amylose.—Two standard digests (*A* and *B*) of amylose (B.V. 1·24) were prepared and incubated respectively with crystalline and stock soya-bean β-amylases at pH 4·8. After the limiting conversion into maltose had

TABLE 3. *The stabilities of crystalline sweet-potato and stock soya-bean β-amylases at various* pH *values.*

	Crystalline β-amylase.		Stock soya-bean β-amylase.		
pH	4·8	6·5	3·6	4·8	6·5
Time (hr.)	Units of β-amylase per ml. of digest :				
0	26	26	26	26	26
5	—	—	20	—	—
24	20	16	—	18	24
48	—	9	—	13	—
72	16	—	—	10	—

TABLE 4. *Action of crystalline and stock soya-bean β-amylases on amylose* (B.V. 1·24) *at* pH 3·6.

	Crystalline β-amylase		Stock soya-bean β-amylase	
Time of incubation (hr.)	Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)
1	69·9	—	67·9	—
2	70·7	0·287	69·7	0·293
5	71·2	—	69·7	0·293
24	Enzyme added equivalent to 26 units/ml.		—	—
26	71·1	—	—	—
28	71·4	0·269	—	—

TABLE 5. *Action of crystalline and stock soya-bean β-amylases on potato starch* (B.V. 0·470) *at* pH 4·8.

Time of incubation (hr.)	Crystalline β-amylase		Stock soya-bean β-amylase	
	Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)
0·17	48·5	—	—	—
0·33	52·0	—	58·0	—
2·0	53·2	0·208	60·0	0·122
5·2	53·9	0·208	60·5	0·117
24·0	57·1	0·175	61·0	0·118
48·0	56·1	0·195	61·0	0·118

TABLE 6. *Action of crystalline and stock soya-bean β-amylases on amylopectin* (B.V. 0·193) *at* pH 3·6, 4·8, *and* 6·5.

	Time of incubation (hr.)	Crystalline β-amylase		Stock soya-bean β-amylase	
		Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)
At pH 3·6:	1	—	—	51·5	—
	2	51·8	0·106	51·7	—
	3	—	—	51·8	0·103
	6	Enzyme added equivalent to 26 units/ml.		—	—
	6·4	51·8	0·108	—	—
At pH 4·8:	0·17	48·0	—	51·5	—
	0·33	49·7	—	51·5	—
	2·0	52·1	0·110	52·4	0·114
	5·2	51·6	0·118	53·4	0·111
	24·0	54·0	0·104	54·8	0·112
	48·0	53·0	0·108	54·3	0·108
	72·0	54·0	0·109	54·5	0·111
At pH 6·5:	0·5	—	—	51·2	—
	1·1	—	—	52·0	—
	2·2	—	—	54·5	0·110
	3	52·0	0·105	—	—
	24·7	—	—	62·7	0·089
	40	54·4	0·105	—	—
	48·8	—	—	69·6	0·059
	80	54·2	0·102	—	—

been attained in both digests, two portions (25 ml. each) were removed from digest *A* and were treated respectively with crystalline β-amylase (0·25 ml.; 650 units) and the equivalent amount of stock soya-bean β-amylase. To a portion (25 ml.) of digest *B* was added the same amount of the latter enzyme preparation. Further measurements of reducing power were then made (see Fig. 1).

Effect of Added Maltose or Amylose on the β-Amylolysis of Amylose.—Amylose (B.V. 1·24) was hydrolysed with crystalline β-amylase at pH 4·8 until the arrest point was attained. A portion of the digest (25 ml.) was then mixed with maltose solution (5 ml.; 51 mg.) and β-amylase solution (0·25 ml.; 990 units). The maltose concentration was thereby increased from 0·33 to 2·01 mg./ml. The lack of effect of this added maltose is shown in Table 7.

TABLE 7. *Effect of added maltose on the β-amylolysis of amylose.*

Time of incubation (hr.)	3·7	5·3	23·6	Maltose added here	27·8	29·2
Conversion into maltose (%)	66·9	67·5	67·6		68·0	68·0

In a similar manner it was shown that when amylose, instead of maltose, was added to a digest of β-amylase and amylose, in which limiting conversion had been attained, the limit of conversion of the added amylose was the same (69%).

β-Amylolysis Limits of an Amylose stored at pH 6·5.—A solution of amylose (B.V. 1·47; 0·598 mg./ml.) in citrate buffer (pH 6·5) was incubated at 35·4° under a layer of toluene. At intervals, portions of the solution were removed and incubated with crystalline β-amylase solution under standard conditions, the reducing power and A.V. (680 mμ) at the arrest point of action being determined (see Table 8).

TABLE 8. *β-Amylolysis of amylose kept at* pH 6·5 *and* 35·4°.

Age of solution (days)	At arrest point: Conversion into maltose (%)	At arrest point: A.V. (680 mμ)	Age of solution (days)	At arrest point: Conversion into maltose (%)	At arrest point: A.V. (680 mμ)
0	67·0	0·394	9	72·5	0·330
1	67·5	0·394	15	71·5	0·315
5	71·5	0·347			

Alkali-treatment of Amylose Limit β-Dextrin.—Amylose (B.V. 1·43) was hydrolysed under standard conditions by crystalline β-amylase at pH 4·8 and 35·4°, and after 2·75 hours a portion of the digest (25 ml.) was removed and N-sodium hydroxide (7·5 ml.) was added. The mixture was heated at 100° for 1 minute, then cooled, and 5N-sulphuric acid (1 ml.) added. β-Amylase solution (0·5 ml.; 650 units) was added at 3 hours from the commencement of the initial incubation and the digest was then incubated at 35·4° (see Table 9).

TABLE 9. *Alkali treatment of amylose limit β-dextrin.*

Initial β-amylolysis of amylose: Time of incubation (hr.)	Conversion into maltose (%)	A.V. (680 mμ)	β-Amylolysis of alkali-treated dextrin: Time of incubation (hr.)	Conversion into maltose (%)	A.V. (680 mμ)
0	0	1·43	0	—	0·360
0·5	58·1	—	0·25	70·1	0·355
2	69·2	0·381	1	71·0	0·348
5	69·4	0·379	21	71·7	0·341
24	70·3	0·361			

β-Amylolysis by Bernfeld and Gürtler's Method.—A solution of amylose (B.V. 1·46; 52·4 mg.) was prepared by dissolving it in 0·25N-sodium hydroxide (20 ml.) and dilution to 100 ml. A buffer solution of pH 4·52 was prepared by dissolving hydrated sodium acetate (18·5 g.) and acetic acid (10·2 ml.) in a total volume of 250 ml. The buffer solution (4 ml.), water (15·5 ml.), and crystalline β-amylase solution (0·5 ml.; 2500 units) were mixed, and alkaline amylose solution (28·08 ml.) was added at 15 drops/minute with shaking. The temperature was 23°. The addition occupied about 30 minutes and the final pH of the solution was 5·06. To complete the β-amylolysis the digest was incubated at 35·4° until the A.V. (680 mμ) attained a constant value. At this stage the conversion into maltose and residual β-amylase activity were determined (Table 10).

TABLE 10. *β-Amylolysis of amylose* (B.V. 1·46) *by Bernfeld and Gürtler's method.*

Time of incubation (hr.)	0·75	1·3	2·0
Conversion into maltose (%)	—	—	72·3
A.V. (680 mμ)	0·429	0·381	0·384
Units of β-amylase per ml. digest	—	—	33

Hydrolysis of Amylose (B.V. 1·47) *by Crystalline β-Amylase in High Concentration.*—A standard digest (50 ml.) containing amylose (B.V. 1·47) was prepared as above and to it was added 1 drop of the suspension of crystalline β-amylase (approx. 11 000 units). Two such additions were subsequently made as indicated in Table 11. Measurements of reducing power and A.V. (680 mμ) were made during the initial action, but the second and third additions of enzyme caused interference with the copper reagent and therefore only A.V. (680 mμ) was determined. The interference was not eliminated by deproteinisation (method of Somogyi, *J. Biol. Chem.*, 1945, **160**, 69).

TABLE 11. *Hydrolysis of amylose at* pH 4·8 *by crystalline β-amylase in high concentration.*

Time of incubation	Conversion into maltose (%)	A.V. (680 mμ)	Units of enzyme/ml. digest
0	0	1·47	220
2 mins.	53·6	—	—
5 ,,	61·4	—	—
11 ,,	63·0	0·420	—
1·0 hr.	66·1	0·381	—
2·7 hrs.	70·4	—	160
24·0 ,,	70·4	0·350	—
24·5 ,,	1 drop of enzyme suspension added		
25·8 ,,	—	0·327	500
26·0 ,,	1 drop of enzyme suspension added		
27·0 ,,	—	0·280	1000
50·0 ,,	—	0·217	—

A similar experiment was performed with potato amylopectin (B.V. 0·193). Fresh enzyme was added after 93 hours and occasioned no change in the degree of hydrolysis (Table 12). This quantity of enzyme was not sufficient to interfere with the measurement of reducing power.

TABLE 12. *Hydrolysis of amylopectin at* pH 4·8 *by crystalline* β*-amylase in high concentration.*

Age of digest (hr.)	13·5	18·5	35·5	84·5	93 *	110
Conversion into maltose (%)	52·0	54·2	53·4	53·4	—	53·9
A.V. (680 mμ)	—	—	0·110	0·112	—	0·110

* Enzyme added equivalent to 26 units/ml.

Amylolytic Action of Heat-treated Stock Soya-bean β*-Amylase.*—Stock soya-bean β-amylase (268 mg.) was dissolved in water (13·2 ml.), and the insoluble residue removed on the centrifuge; the enzyme concentration was approx. 1300 units/ml. Portions (3 ml.) of the solution were placed in 10-ml. centrifuge tubes and heated for varying times in a water-bath at 63° ± 1°. The tubes were cooled in cold water, toluene was added, and the solutions were stored for 4 days in the refrigerator to allow the *temporarily* inactivated β-amylase to recover its full activity (see succeeding paper, Part XVI). The β-amylase activities were measured and compared with that of an unheated specimen stored under the same conditions. Amylose (B.V. 1·24) was then digested at pH 4·8 with each of the solutions; standard digests were used and the enzyme activity in each was 28 units/ml. The small precipitates formed in the digests containing heated enzyme may have carried down some polysaccharide because the values of A.V. (680 mμ) at the arrest points (Table 13) were lower than was to be expected from the measured conversion into maltose (cf. Table 4).

TABLE 13. *Hydrolysis of amylose* (B.V. 1·24) *at* pH 4·8 *using heat-treated stock soya-bean* β*-amylase.*

Duration of heat treatment (min.)	β-Amylase activity remaining after heat treatment	Conversion of amylose after 17 hr.	A.V. (680 mμ) after 17 hr.
0	100	86·9	0·070
15	63	78·5	0·142
30	50	73·0	0·215
45	40	72·5	0·210

Heat-treatment of Crystalline β*-Amylase.*—Two portions (2·5 ml. each; 15 125 units) of crystalline β-amylase solution were heated at 59° in a water-bath for 10 and 30 minutes. They were cooled, then stored overnight in a refrigerator, and the enzyme activities remaining were found to be 66·5 and 43·9% of the original activity, respectively. The activity of a portion of the original solution stored for the same time was unchanged. This sample, and those which had been heated, were used to hydrolyse amylose (B.V. 1·47) at pH 4·8 and pH 6·5 under the standard conditions (see Table 14).

TABLE 14. *Action of heat-treated crystalline* β*-amylase on amylose* (B.V. 1·47).

	Time of incubation (hrs.)	Conversion into maltose (%)		
		Unheated enzyme	Enzyme at 59° for 10 min.	Enzyme at 59° for 30 min.
At pH 6·5	2·3	71·5	71·0	71·5
	14·0	73·3	74·3	77·5
	38·5	84·0	81·5	86·6
At pH 4·8	2·3	71·5	70·1	70·1
	14·0	71·1	67·6	70·8
	38·5	74·6	72·5	72·5

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129. *The Enzymic Synthesis and Degradation of Starch. Part XVI.* The Purification and Properties of the β-Amylase of Soya Bean.*

By Stanley Peat, S. J. Pirt, and W. J. Whelan.

A method is described for the purification of the β-amylase of soya bean, the product of which is amorphous but is virtually free from Z-enzyme as well as from α-amylase and maltase. The elimination of Z-enzyme has been studied in detail and it is shown that for the structural analysis of amylaceous polysaccharides the purified soya-bean β-amylase is exactly equivalent to the crystalline enzyme of sweet potato.

It is established that the amyloses of sago, tapioca, and maize are branched in the same way as potato amylose and that the branch points are attacked by Z-enzyme.

It was shown in Part XV * that soya-bean β-amylase as ordinarily prepared is a mixture of an enzyme similar to the crystalline β-amylase of sweet potato, and Z-enzyme, which supplements the β-amylolysis of amylose. The purpose of the present investigation was to isolate the β-amylase of soya bean in a form free from all other starch-degrading enzymes, and to compare its action with that of the crystalline enzyme from sweet potato.

Initial Purification of Soya-bean β-Amylase.—An initial concentrate of β-amylase was prepared by the successive steps summarised in Table 1, namely, (*a*) aqueous extraction of defatted bean flour, (*b*) isoelectric precipitation of inactive protein, (*c*) heat treatment to remove Z-enzyme (see below), (*d*) precipitation of β-amylase by means of acetone (Newton, Naylor, and Hixon, *Cereal Chem.*, 1939, **16**, 71; Meyer, Fischer, and Piguet, *Helv. Chim. Acta*, 1951, **34**, 316), and (*e*) reprecipitation with ammonium sulphate followed by dialysis (Balls, Walden, and Thompson, *J. Biol. Chem.*, 1948, **173**, 9). Precipitation with acetone served to concentrate the enzyme but not to increase its purity and was therefore omitted in later work. The factor of purification from aqueous extract to final concentrate was 5·8. The product contained negligible amounts of α-amylase and maltase and at 0° the dialysed solution retained its activity over several months.

Table 1. *Initial purification of soya-bean β-amylase.*

Operation	Recovery of β-amylase (%)	Units of enzyme/mg. of protein-N
Ground, defatted soya beans (955 g.) extracted for 2 hours with H_2O (4775 ml.). Residue discarded	100	429
pH adjusted to 4·8 with N-H_2SO_4 (82·5 ml.). Ppt. discarded	81	794
Temperature held at 60—61° for 30 minutes. Ppt. discarded	61	1060
pH adjusted to 6·3 with N-aq. NH_3 (50 ml.), solution cooled to 0°, acetone (2 volumes) added, and ppt. dissolved in H_2O (650 ml.)	48	1060
Aq. $(NH_4)_2SO_4$ (saturated; pH 6·0; 2 vols.) added at room temp. Ppt. centrifuged and dissolved in H_2O (120 ml.; 0°). Soln. dialysed against distilled H_2O for 48 hr.	35	2510

Removal of Z-Enzyme.—Z-Enzyme is partly separated from β-amylase when the method of purification given in Table 1, but without the heat treatment, is used. When amylose (B.V. 1·24) was hydrolysed by such a preparation the conversion limit was 75%, compared with 86% for the unpurified enzyme preparation. To achieve complete removal of Z-enzyme from β-amylase, use was made of the fact that Z-enzyme is more heat-labile than β-amylase (see Part XV) and, in order to follow the inactivation of Z-enzyme by this process, a method of measuring its activity was devised. Amylose was hydrolysed to the point of limiting conversion with crystalline β-amylase and to the resulting solution of amylose limit β-dextrin at pH 4·8 (still containing active β-amylase) was added the preparation under test. If the latter contained Z-enzyme, the Z-labile links of the limit β-dextrin were removed and the β-amylase present was enabled to effect further hydrolysis

* Part XV, preceding paper.

and consequent further diminution in the iodine absorption. The effect on amylose limit β-dextrin of the addition of a stock soya-bean preparation is shown in Fig. 1. The experiments to determine the conditions for the removal of Z-enzyme were carried out on a bean preparation after isoelectric precipitation (Table 1). The solution was heated at 63° for varying times and at various pH values, and the amounts of β-amylase and Z-enzyme remaining were estimated. The results show that at pH 5·5 β-amylase and Z-enzyme are equally thermostable.

FIG. 1. *Action of crystalline and stock soya-bean β-amylases on amylose limit β-dextrin at* pH 4·8.

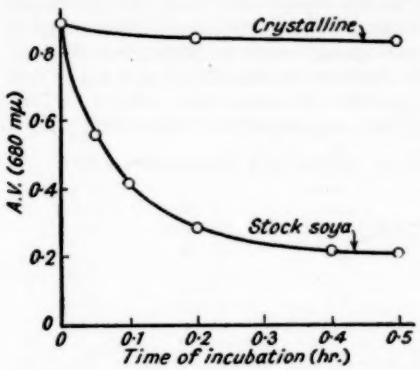


FIG. 2. *Relative heat stabilities of Z-enzyme and β-amylase at* pH 4·8. *Time of heating* = 30 *min.*

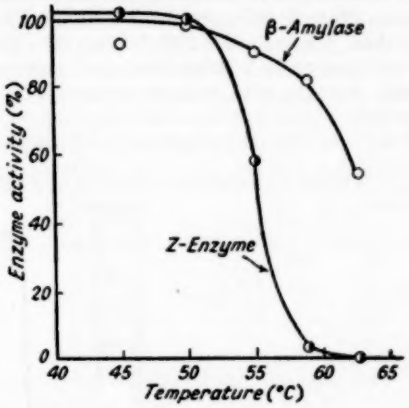


FIG. 3. *Optimum time of heating at* 62° *and* pH 4·8 *for inactivation of Z-enzyme.*

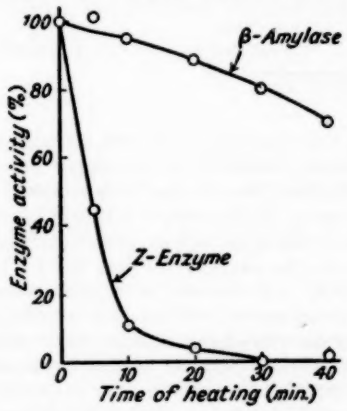
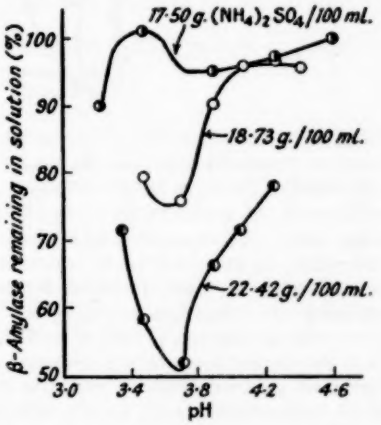


FIG. 4. *The* pH *of minimum solubility of β-amylase in ammonium sulphate solution.*



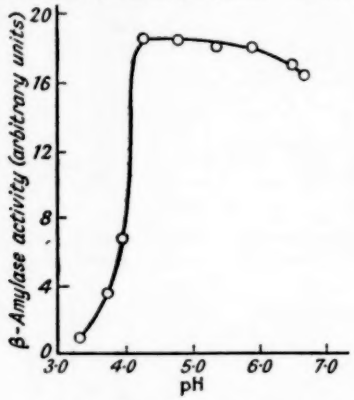
Inactivation of Z-enzyme is therefore best effected at a pH value removed from 5·5, and pH 4·8 was chosen since this is also the pH of the solution after isoelectric precipitation. The optimum temperature (60°) and optimum time (30 minutes) for removal of Z-enzyme were deduced from the data of Figs. 2 and 3 respectively, and these conditions were observed in the large-scale purification.

Balls *et al.* (*loc. cit.*) included a short heat treatment in their method of purification but did not state the reason for doing so. This treatment, it now seems, was of considerable importance in freeing the preparation from Z-enzyme. It was also reported that it reversibly inactivated the sweet potato β-amylase. This was also true of the soya-bean

enzyme before isoelectric precipitation (Table 7, p. 720), but the inactivation was irreversible at a later stage in the purification and under the conditions used for the removal of Z-enzyme.

Final Purification of the β-Amylase Concentrate.—At an early stage in the purification of soya-bean β-amylase an attempt was made to crystallise the enzyme from a concentrated solution under the conditions used for the crystallisation of sweet potato β-amylase, *i.e.*, by ammonium sulphate fractionation at pH 3·6—3·7. As the attempt was unsuccessful the modification was introduced of precipitating the β-amylase at its pH of minimum solubility in ammonium sulphate solution, since this method was applied with success by Distèche in crystallising several of the enzymes in a muscle extract (*Biochim. Biophys. Acta*, 1948, **2**, 265), and by Schwimmer and Balls in the crystallisation of malt α-amylase (*J. Biol. Chem.*, 1949, **179**, 1063). The pH of minimum solubility of soya-bean β-amylase was found to be 3·70 by Distèche's method with ammonium sulphate buffered to constant ionic strength with sodium acetate (Fig. 4). The further purification of the initial concentrate (Table 1) was achieved by repeated precipitation with ammonium sulphate (17·0—27·0 g. per 100 ml.) at pH 3·70. This process did not progressively increase the purity of

FIG. 5. *Optimum* pH *of purified soya-bean β-amylase. Temperature of incubation* = 35°.



the enzyme; the value rose to about 9000 β-amylase units per mg. of protein-nitrogen and thereafter remained constant (Table 2). At first, this appeared to be the upper limit of purification of the soya-bean β-amylase since the same limit was reached independently of variations in the initial purification process or in the range of ammonium sulphate concentration used. A preparation which had attained this limiting value was, however, further fractionated by the addition of ammonium sulphate to the enzyme solution, until a precipitate began to form, followed by cooling to −1·5°. A fraction was thus isolated containing the β-amylase in high yield (74%) and having an activity of 14 900 units per mg. of protein-nitrogen (Table 8, p. 721) representing an overall purification factor of 35. This is the purest preparation obtained in the present work. None of the fractions could be induced to crystallise by methods in which the precipitant (ammonium sulphate or alcohol) was added slowly to a concentrated solution of β-amylase, either by dropwise

TABLE 2. *Fractionation of soya-bean β-amylase with ammonium sulphate at* pH 3·7.

Operation	Limits of $(NH_4)_2SO_4$ concentration (g./100 ml.)	β-Amylase units/ml.	β-Amylase units/mg. of protein-N	Recovery of enzyme (%)
Concentrate prepared as in Table 1 (337 ml.)...	—	10 200	3440	100
Precipitation 1. Ppt. dissolved in H_2O (81 ml.)	16·5—27·0	20 200	5950	75
Precipitation 2. Ppt. dissolved in H_2O (18 ml.)	17·0—24·0	49 000	8100	51
Precipitation 3. Ppt. dissolved in H_2O (9 ml.)	17·5—24·0	83 500	8930	43
As 3	17·5—24·0	55 000	8600	35
As 3	17·5—24·0	61 000	9350	26

addition or by diffusion through a Cellophane membrane. An approximate determination of specific activity carried out on the sample of crystalline β-amylase in our possession gave a value of 41 000 units per mg. of protein-nitrogen. It appears therefore that the soya-bean preparation is still capable of further purification. It was, however, decided at this stage to examine the purified enzyme with respect to its action on starch polysaccharides.

Properties of Purified Soya-bean β-Amylase.—A sample having an activity of 8700 units, prepared as in Tables 1 and 2, was used. The pH dependence of the activity of the enzyme is depicted in Fig. 5. Soya-bean β-amylase exhibits the same broad range of optimum activity as does the sweet-potato enzyme. The action of the enzyme on potato starch and its fractions was studied at pH 4·8 (Table 3). The progress of reaction was followed by means of the A.V. (680 mμ) of the iodine-stained digest determined at intervals until the arrest point was reached, the percentage conversion into maltose being measured at this point. Table 3 shows that the arrest point in the case of amylose is reached within

TABLE 3. *Amylolytic action of purified soya-bean β-amylase at* pH 4·8.

	Amylose (B.V. 1·47)		Potato starch (B.V. 0·470)		Amylopectin (B.V. 0·193)	
Age of digest (hours)	A.V. (680 mμ)	Conversion into maltose, %	A.V. (680 mμ)	Conversion into maltose, %	A.V. (680 mμ)	Conversion into maltose, %
1·0	0·419	—	0·209	—	0·128	—
2·0	0·411	—	0·205	—	0·119	—
3·0	0·425	67·7	0·199	53·0	0·108	51·0
20·0	0·397	—	0·183	54·5	0·119	53·3
44·0	0·362	70·4	—	—	—	—

an hour. The freedom of the sample from Z-enzyme is indicated by the very slow fall in A.V. (680 mμ) after the arrest point has been reached. These results, when compared with those of Figs. 1 and 2 in Part XV (preceding paper) demonstrate the complete parallelism in action between purified soya-bean β-amylase and the crystalline sweet-potato enzyme. The results in Table 4 defined the arrest points of action on potato starch and

TABLE 4. *Amylolytic actions of sweet potato, purified and stock soya-bean preparations.*

	Amylose (B.V. 1·47)		Potato starch (B.V. 0·470)		Amylopectin (B.V. 0·193)	
Enzyme prepn.	A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point	A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point	A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point
Crystalline sweet potato	0·41	68	0·20	53	0·11	52
Purified soya	0·42	68	0·20	52	0·11	51
Stock soya	0·06	97	0·12	61	0·11	53

its components of these two preparations of β-amylase and also of stock soya-bean preparation which contains Z-enzyme in addition. It would seem probable that all β-amylase preparations which bring about the complete conversion of potato amylose will be found to contain Z-enzyme as well as β-amylase.

It may well be that the supposed linear components of other starches also possess these Z-labile anomalous linkages. We have in fact shown that the amyloses of sago, tapioca, and maize are incompletely hydrolysed by pure β-amylase whereas the stock soya-bean enzymes (β-amylase + Z-enzyme) effect almost complete conversions of these samples of amylose (Table 5). Furthermore, the presence of these anomalous linkages may be detected by phosphorylase action. In the following paper (Part XVII), it is shown that potato phosphorylase can, in the absence of Z-enzyme, convert only 70% of amylose into glucose-1 phosphate; in the presence of added Z-enzyme the conversion is almost 100%.

The data given in Table 3 indicate the virtual absence from the purified soya-bean β-amylase of Z-enzyme and α-amylase action at pH 4·8. Maltase was present in traces; approximately 1% of maltose was hydrolysed at pH 4·8 in each 10 hour period of incubation.

TABLE 5. *β-Amylolysis of amyloses from different plant sources.*

Plant source of amylose	Blue value	Purified soya-bean β-amylase		Stock soya-bean enzymes	
		A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point	A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point
Potato	1·47	0·42	68	0·06	97
Sago	1·41	0·36	70	0·09	90
Tapioca	1·37	0·33	70	0·07	90
Maize	1·26	0·31	68	0·08	86

The values of percentage conversion, into maltose, of the polysaccharides given in Table 3 are corrected for this maltase activity.

Influence on the Conversion Limit of the Method used to dissolve Amylose.—A series of control experiments were made with a view to determining the influence of various methods of dissolution on the conversion limit of amylose. The four methods chosen were (*a*) dissolution in 0·25N-sodium hydroxide followed by neutralisation (HCl) and buffering to pH 4·8; (*b*), as (*a*) except that acid and buffer were mixed before being added to the alkaline amylose solution; (*c*) dissolution in water at 100°; and (*d*) autoclaving at 126° in unbuffered aqueous solution. The dissolved amyloses were then hydrolysed at pH 4·8 by the purified and the stock soya-bean preparations (Table 6).

TABLE 6. *β-Amylolysis of amylose dissolved by different methods.*

Method of dissolving amylose *	Blue value †	Purified soya-bean β-amylase		Stock soya-bean β-amylase	
		A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point	A.V. (680 mμ) at arrest point	Conversion into maltose, % at arrest point
(*a*)	1·45	0·371	68·5	0·058	92·0
(*b*)	1·47	0·363	68·0	—	—
(*c*)	1·49	0·420	66·6	0·060	89·0
(*d*)	1·49	0·423	66·4	0·055	88·5

* See text. † After buffering of amylose to pH 4·8 (see Part XV, Experimental section).

It is seen that the method used in dissolving the amylose has but small influence on the amounts of maltose liberated by either purified or stock soya-bean preparations. The possibility that the anomalous linkage in the amylose molecule which arrests the progress of β-amylase is an artifact introduced by alkali treatment is therefore ruled out. That precautions are necessary when using alkali is indicated by the data in Table 9 (p. 722), from which it is seen that prolonged treatment of amylose with alkali at 100° *raises* the conversion limit of amylose attained with the purified enzyme, probably because of alkali-induced fragmentation of the amylose chains. The fall in blue value of the amylose which accompanies the treatment with alkali and the decrease in glucose recoverable on acid hydrolysis are indications of such degradation.

This investigation serves to establish (i) the occurrence in the amylose chains of anomalous structures which impede β-amylolysis, and (ii) the presence in a stock β-amylase preparation of an enzyme (Z-enzyme) which eliminates these barriers. Discussion of the related problems of the nature of these anomalous linkages in amylose and of the action of Z-enzyme upon them is reserved for the paper which follows (Part XVII) since in the latter is described the isolation of Z-enzyme free from both α- and β-amylase.

EXPERIMENTAL

Analytical Methods.—(a) *General.* The methods by which starch fractions have been prepared, together with details of the technique used in β-amylolysis are given in Part XV (preceding paper). Purified soya β-amylase was stored as a suspension in ammonium sulphate solution (pH 3·7; see below), drops of which were diluted with water for measurement of the activity of the solution before use. The enzyme protein did not interfere with measurement of reducing power; deproteinisation was therefore unnecessary.

(b) *Determination of protein-nitrogen.* Soya-bean flour was extracted with water and divided into two portions. One of these was taken to dryness and the nitrogen content was determined by Ma and Zuazaga's method (*Ind. Eng. Chem., Anal.*, 1942, **14**, 280) with the apparatus described by Redemann (*ibid.*, 1939, **11**, 635). The other portion was used to calibrate the biuret reagent of Gornall, Bardawill, and David (*J. Biol. Chem.*, 1949, **177**, 751). From the results of both determinations a curve was plotted relating the colour developed by the biuret reagent to the nitrogen content of the protein. It was confirmed that interference with the colour reagent by ammonium sulphate was suppressed by the addition of sodium hydroxide solution.

(c) *Determination of density of ammonium sulphate solution.* The gradient-tube method of Buchanan and Arfinsen (*ibid.*, 1949, **180**, 47), which requires one drop of the solution under test, was used.

Initial Purification of Soya-bean β-Amylase (Table 1).—(a) *Extraction of soya flour.* Control experiments showed that the maximum yield of β-amylase was achieved by shaking the ground and ether-defatted soya beans (see preceding paper) with water for 2 hours. Extracts prepared by shaking for longer periods showed a progressively diminishing activity.

(b) *Isoelectric precipitation of inactive protein.* An aqueous extract of soya beans was prepared as in (a), the pH of which was 6·3. Portions of this extract were acidified to various pH values with 0·1N-sulphuric acid. The weights of protein precipitate and the β-amylase activity remaining in solution were measured. The results showed that precipitation was optimal at pH 4·8 and that a constant recovery of β-amylase (88%) was obtained at pH values greater than 4·6; at more acid pH values the recovery decreased steadily, being 47% at pH 3. Removal of inactive protein and recovery of β-amylase were therefore both maximal at pH 4·8.

(c) *Elimination of Z-enzyme.* Amylose (B.V. 1·24; 425 mg.) was hydrolysed under standard conditions by crystalline β-amylase at pH 4·8 in a digest of total volume 500 ml. Portions were removed at intervals for the measurement of A.V. (680 mμ) and reducing power. When the conversion limit had been reached the digest was heated on a boiling water-bath for 20 minutes, cooled, and rediluted to 500 ml. with 0·015M-acetate buffer (pH 4·8). The solution of amylose limit β-dextrin so prepared was stored under toluene.

The method of determining Z-enzyme activity comprised the preliminary measurement of the β-amylase activity of the solution under test, adjustment of the concentration of enzyme to 660 units of β-amylase per ml., and the addition of this solution (1 ml.) to the amylose limit dextrin solution (25 ml.) at 35·4°. Measurements of A.V. (680 mμ) were made at intervals by diluting a portion (5 ml.) of the digest to 100 ml. with standard iodine solution (1 ml.), 5N-hydrochloric acid (3 drops), and water. The activity of Z-enzyme was expressed in terms of the fall in A.V. (680 mμ) which occurred during the first 30 minutes' incubation of the above digest. It should be noted that this method of testing for Z-enzyme does not distinguish it from α-amylase. The original aqueous bean extract did not, however, cause any significant degradation of amylopectin limit β-dextrin at pH 4·8, a sensitive test for α-amylase with which Z-enzyme does not interfere. The assumption that, under the above conditions, the hydrolysis of amylose limit β-dextrin is initiated by Z-enzyme is therefore justified.

An aqueous extract of defatted soya flour was purified by isoelectric precipitation, and portions (25 ml.) of this extract were treated by the various methods indicated below and cooled to 15°, and, if necessary, the pH was adjusted to 6·1—6·5. After the mixture had been kept for 3 days at +2°, 0·2M-acetate buffer (pH 4·8) was added to 0·033M-concentration, and any precipitate was discarded. The β-amylase and Z-enzyme activities remaining in solution were then determined and compared with the activities in control portions of the original extract which had been stored for the same time but were otherwise untreated. It was always observed that heat-treated solutions of soya β-amylase caused an immediate and reproducible fall of 0·2 in the A.V. (680 mμ) of the amylose limit β-dextrin. The fall was due to precipitation of the dextrin by protein since part of the blue iodine complex could be filtered off from the iodine solution. The apparent Z-enzyme activity was due entirely to this precipitation of polysaccharide since, after the initial fall, the A.V. (680 mμ) remained constant. Allowance has been made for this factor in calculating the results given in Figs. 2 and 3. The co-precipitation effect was peculiar to enzyme solutions at this stage in the purification. It was not observed with soya β-amylase after final purification. To determine the effect of pH on the enzyme activities portions of the extract were adjusted to various pH values by the addition of either N-sulphuric acid or N-ammonia, and the solutions were heated for different times at 63°. After 15 minutes' heating at pH 4·45, 6·43, and 7·46, Z-enzyme activity had disappeared. Only at pH 5·53 did the Z-enzyme activity persist for more than 30 minutes; and even in this

case it was eliminated after storage at 63° for 50 minutes. The effect of temperature was determined by heating portions of the extract on a water-bath for 30 minutes over a range of temperatures (Fig. 2); the time of heating at 62° was also varied (Fig. 3).

TABLE 7. *Reversible heat inactivation of soya-bean β-amylase.*

Time of heating at 60° (min.)	1	4·7	9·3	15	19·8
Enzyme activity recovered immediately after heating (%)	102	80·5	61	55	56
Enzyme activity recovered after 4 days at 3° (%)	99	98	94	93	96

Heat inactivation of soya-bean β-amylase. An aqueous extract of defatted soya flour was prepared and a portion (150 ml.; pH 6·3) heated on a water-bath at 60°. Portions (25 ml.) of this heated solution were removed at intervals, then cooled rapidly, and the β-amylase activities determined immediately and after storage for 4 days at 3°. The activity of an unheated portion was determined at the same times and the percentage recoveries of the enzyme estimated (Table 7). When a bean extract (pH 4·8), purified by isoelectric precipitation, was heated at 60° for 15 minutes the loss in activity was much less than in the above experiment, being 10% compared with 45%. No regeneration of activity was, however, observed when this solution was stored at 3°.

(d) *Precipitation with acetone.* To portions (10 ml.) of aqueous bean extracts before and after isoelectric precipitation were added varying amounts of acetone up to 65% by volume, the whole operation being conducted at 0°. The suspensions were centrifuged and the precipitates dissolved in water (25 ml.) for estimation of β-amylase activity (see below). The results show that before isoelectric precipitation the enzyme is precipitated at a much lower concentration of acetone. Presumably the enzyme is co-precipitated with the inactive protein removed by isoelectric precipitation.

Concn. of acetone (%)	20	30	40	50	60	70	80	89·5
Enzyme pptd. (%) Before isoelectric pptn.	76	91	87	99	99·5	104	100	99·5
Enzyme pptd. (%) After isoelectric pptn.	3·5	—	26·1	—	92	—	89	—

(e) *Precipitation with ammonium sulphate.* An aqueous extract of soya β-amylase was purified by isoelectric precipitation and acetone precipitation as in Table 1. To portions of this purified extract were added increasing amounts of saturated ammonium sulphate solution (pH 6·0), and after removal of the precipitate the amount of enzyme remaining in solution was determined.

Concn. of $(NH_4)_2SO_4$ (g./100 ml.)	6·4	12·7	19·1	25·4	31·9	37·3
Enzyme pptd. (%)	9·6	10·0	11	15	86	86

(f) *Final method.* The method finally adopted differed in two respects from that given in Table 1. First, lack of adequate refrigeration facilities caused inactivation of β-amylase when the acetone precipitation was carried out on a large scale. This stage was therefore omitted. Secondly, the use of large volumes of ammonium sulphate in the succeeding stage of purification was avoided by adding the required amount of solid ammonium sulphate to the enzyme solution with stirring until dissolved. The modified method may therefore be summarised as follows. Ether-defatted soya flour was shaken with water (5 ml./g. of flour) for 2 hours, octyl alcohol (0·1 ml./l.) being added to prevent foaming. The suspension was centrifuged and to the supernatant solution was added N-sulphuric acid (3·23 ml./100 ml.) to bring the pH to 4·8. The precipitate was removed on the centrifuge and the solution heated at 60—61° for 30 minutes. After cooling, the precipitate was centrifuged and rejected. Ammonium sulphate ("AnalaR"; 41·8 g./100 ml.) was added slowly with stirring. The precipitate was centrifuged and dissolved, 10 ml. of water being used for each 250 ml. of original ammonium sulphate solution. The enzyme solution was dialysed against running distilled water for 36—48 hours, and then stored under toluene in the refrigerator. All operations, except where otherwise stated, were carried out at room temperature. In a typical preparation by this method the overall recovery of β-amylase activity was 78% and the specific activity was 2610 units per mg. of protein-nitrogen (cf. Table 1).

Final Purification of β-Amylase.—(a) *Determination of* pH *of minimum solubility.* The method is based on that of Distèche (*loc. cit.*). Ammonium sulphate solutions containing acetate buffer of ionic strength 0·0725 were prepared, the amounts of acetic acid and sodium acetate required being calculated from the nomogram prepared by Boyd (*J. Amer. Chem. Soc.*,

1945, **67**, 1035). The pH values of portions diluted to half strength were determined. A solution of soya β-amylase was prepared by the process described above. To portions (4 ml.), contained in 10-ml. centrifuge tubes at 20°, were added with stirring portions (4 ml.) of the buffered ammonium sulphate solutions. The precipitates were removed on the centrifuge and the activity of β-amylase remaining in solution was determined. By comparison with the initial enzyme activity the amount of enzyme in the precipitates was calculated. It was verified that the pH of the ammonium sulphate solution did not change on dilution with the enzyme. The curves depicting the amounts of β-amylase remaining in solution at various values of pH and ammonium sulphate concentration are given in Fig. 4, which shows that the pH of minimum solubility is 3·7.

(b) *Fractional precipitation of β-amylase.* A solution of pH 3·70 was prepared containing ammonium sulphate (490 g.), hydrated sodium acetate (9·86 g.), and glacial acetic acid (29·2 ml.) per litre. This was used as the precipitant for β-amylase in the fractionation procedure outlined in Table 2. To the enzyme solution was added ammonium sulphate to the lower limit of concentration given in Table 2, any precipitate being rejected. The enzyme was precipitated by the further addition of precipitant to the stated concentration. The precipitant was always added dropwise, with stirring, during 30 minutes, at 0—5°. The precipitated β-amylase was centrifuged immediately and redissolved in the minimum of ice-cold water. The concentration of ammonium sulphate, arising from that occluded on the precipitate, was determined by the gradient-tube method. Control experiments had shown that at the first and second precipitations by this method the enzyme began to appear in the precipitate at 17 g. of ammonium sulphate/100 ml. and precipitation was complete at 27 g./100 ml. The following results relate to a once-precipitated enzyme.

Concn. of $(NH_4)_2SO_4$ (g./100 ml.)	16	17·5	19	22	24	26
Enzyme pptd. (% of initial activity)	5	8	17	49	73	91·5

(c) *Fractionation by cooling a saturated enzyme solution.* The end product of the fractionation procedure given in Table 2 was sub-fractionated as follows. The precipitate was dissolved in water (5 ml.) at 0° and a small insoluble residue removed in a centrifuge. A turbid solution was obtained which did not become clear on addition of water (4 ml.). The ammonium sulphate concentration was now 11·3 g./100 ml. The temperature of the solution was raised to 9° and buffered ammonium sulphate solution added with stirring until a permanent precipitate was produced. The solution was cooled slowly to −1·5° and after 24 hours the precipitate was centrifuged, yielding a clear solution which was further fractionated in the same manner. Four precipitated fractions and a supernatant solution were obtained which were analysed for β-amylase and protein content (Table 8).

TABLE 8. *Sub-fractionation of soya-bean β-amylase.*

Approx. limits of $(NH_4)_2SO_4$ concn. (g./100 ml.)	Precipitate	
	Units of enzyme/mg. of protein-N	% of original activity
11—16	4580	4
16—18	3970	3
18—19	4480	3
19—21	6850	16
>21	14 900 (supernatant)	74 (supernatant)

Optimum pH *of Purified Soya-bean β-Amylase.*—The activity of the enzyme was determined in the presence of 0·2M-sodium acetate–acetic acid buffers. The total volume of the activity digest was 20·4 ml., containing 2·4 ml. of buffer and other reagents in proportion to the standard amount (Fig. 5).

Action of Purified Soya-bean β-Amylase on Starch Polysaccharides.—The technique was identical with that adopted for crystalline β-amylase (see Part XV, preceding paper). The sample of enzyme used was prepared by the above method of initial purification and was refractionated as in Table 2.

Comparison of Methods of Dissolving Amylose.—The same sample of amylose (B.V. 1·49) was used in the following experiments. (*a*) Amylose (71·3 mg.) was dissolved in the usual way in 0·25N-sodium hydroxide (20 ml.), cooled, and diluted to 50 ml. A portion (25 ml.) was neutralised with N-hydrochloric acid (phenolphthalein), and 0·2M-acetate buffer (pH 4·8; 6 ml.) was added, followed by water to 50 ml. To the remainder of the amylose solution the acid, indicator, and buffer were added as a mixture before dilution to 50 ml. The amyloses were then

submitted to hydrolysis by the stock and the purified preparation of soya-bean β-amylase. The arrest points, attained in 2 hours, are given in Table 6. (*b*) Amylose (66·9 mg.) was wetted with benzene (0·45 ml.) and dissolved in water (60 ml.) on a boiling water-bath. After 10 minutes' heating the amylose had dissolved to give a faintly turbid solution; the heating was continued for a further 20 minutes. The solution was diluted to 100 ml. with water and acetate buffer to 0·024M-concentration and the amylose was then hydrolysed as in (*a*). (*c*) An amylose solution (pH 6·7), prepared as in (*b*), was placed in an autoclave which was raised to 20 lb./sq. in. pressure (126°) in 25 minutes and kept at this pressure for 30 minutes. After cooling, the solution was treated as in (*b*) (see Table 6).

Action of Alkali on Amylose.—Amylose (B.V. 1·49; 111 mg.) was dissolved in water (45 ml.) at 100° as under (*b*) above, cooled, and diluted to 50 ml. Portions (4·5 ml.) were added to 10-ml. flasks, followed by 2N-sodium hydroxide (0·645 ml.), giving a final concentration of 0·25N-alkali. The flasks were heated on a boiling water-bath for varying times and then cooled rapidly. The solutions were neutralised (N-hydrochloric acid); 0·2M-acetate buffer (pH 4·8; 1·2 ml.) and water to 10 ml. were then added. A portion (1 ml.) was used for determination of B.V. and the remainder for incubation with purified soya β-amylase, the arrest points, attained within 2 hours, being determined (see Table 9).

TABLE 9. *Treatment of amylose with* 0·25N-*sodium hydroxide at* 100°.

Time of heating in alkali (min.)	B.V.	Conversion into maltose (%) at arrest point	A.V. (680 mμ) at arrest point	Polysaccharide remaining * (%)
0	1·47	63·5	0·420	100
1·5	1·45	66·5	—	—
3	1·45	67·2	0·369	—
5	1·48	67·8	0·350	100·9
8	1·45	69·1	0·325	—
10	—	—	—	98·1
12	1·37	72·7	0·220	—
15	—	—	—	93·2
17	1·35	74·0	0·170	—
20	—	—	—	95·8
30	—	—	—	88·2
40·3	—	—	—	82·5

* See Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.

We are grateful to Dr. R. S. Higginbotham for specimens of sago and tapioca amylose and to Dr. T. J. Schoch for the sample of maize amylose.

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130. *The Enzymic Synthesis and Degradation of Starch. Part XVII.* Z-Enzyme.*

By STANLEY PEAT, GWEN J. THOMAS, and W. J. WHELAN.

Z-Enzyme, which supplements the action of β-amylase or phosphorylase on amylose, has been isolated from the soya bean as a freeze-dried powder free from α- and β-amylases. Its function is the hydrolysis of the limited number of branch links in amylose which act as barriers to β-amylolysis or phosphorolysis. Z-Enzyme is shown to be a β-glucosidase and its action on amylose is simulated by the β-glucosidase of sweet almonds.

The form of the β-glucosidic links in amylose is discussed.

THE evidence cited in the two preceding papers has shown that the complete conversion of amylose into maltose is effected by a mixture of two enzymes, namely, β-amylase and Z-enzyme. It is the function of the former enzyme to liberate maltose and of the latter to remove, by hydrolysis, anomalous structures within the amylose molecule which impede the endwise attack of β-amylase. In the absence of Z-enzyme, β-amylase converts only 70% into maltose. Z-Enzyme is associated with β-amylase in stock soya-bean β-amylase

* Part XVI, preceding paper.

and is probably to be found in β-amylase preparations from other plant sources. The present communication describes the isolation of Z-enzyme as a dry powder, entirely free from α- and β-amylases. Its properties are recorded and evidence is afforded which identifies it as a β-glucosidase. A preliminary account of some of the following observations has been given by Thomas, Whelan, and Peat (*Biochem. J.*, 1950, **47**, xl).

The possibility existed that the structures in amylose impeding β-amylolysis consisted of ester-phosphate groups. Posternak (*J. Biol. Chem.*, 1951, **188**, 317) has shown, for example, that ester-phosphate groups are present in the dextrins formed in the α-amylolysis of potato starch and that these obstruct the action of β-amylase on the dextrins. Although these dextrins were probably derived from the amylopectin component, potato amylose does contain esterified phosphorus in an amount corresponding to 1 atom of phosphorus per 2400 glucose residues. This quantity, although very small, would account for the observed effects if one-third of the amylose molecules contained an ester phosphate group situated at or near the non-reducing end. If this explanation were correct then Z-enzyme would be a phosphatase. Stock soya-bean β-amylase contains a phosphatase which can be detected by its action on sodium glycerophosphate. This phosphatase is not present in purified soya β-amylase, which is also free from Z-enzyme (see Part XVI). It was, however, demonstrated in the following manner that Z-enzyme is not a phosphatase. First, pre-treatment of potato amylose with bone phosphatase (which, according to Thoai, Roche, and Silkol-Bernère, *Compt. rend.*, 1946, **223**, 931, will dephosphorylate starch) had no effect on the limit of β-amylolysis (Table 3). Secondly, stock soya-bean β-amylase was fractionated on a paper chromatopile, from which Z-enzyme and phosphatase were eluted together by ammonium sulphate solution; the β-amylase was not extracted from the pile even by perfusion for 10 days. When the eluates were kept at room temperature for two weeks, they lost Z-enzyme activity, but phosphatase activity persisted. Finally, Z-enzyme was isolated, by the following procedure, as a freeze-dried powder which exhibited no phosphatase activity. The isolation of Z-enzyme free from associated enzymes was achieved as a result of an attempt to eliminate the α-amylase component of soya bean by a modification of the method of Blom, Bak, and Braae (*Z. physiol. Chem.*, 1936, **241**, 273), who effected the preferential destruction of α-amylase by the treatment of an impure malt β-amylase with acid at 0°. When the pH of the stock soya-bean preparation was adjusted to 3·0 and the solution kept at 35°, instead of at 0°, both α- and β-amylases were destroyed, but Z-enzyme activity was not appreciably diminished (Table 4, p. 728). The phosphatase was partly destroyed by this treatment and after the solution had been freeze-dried no phosphatase remained, although Z-enzyme was unaffected. Potato phosphorylase is similarly inactivated by being freeze-dried in the absence of buffer (Part VI, *J.*, 1950, 84).

Function of Z-Enzyme in the β-Amylolysis of Amylaceous Polysaccharides.—Having regard to their apparent similarity of function, particular emphasis is placed on the necessity to distinguish Z-enzyme from α-amylase. For this purpose a solution of salivary α-amylase was prepared and so diluted that it exerted only a slight action on amylose and amylopectin during several hours. Table 1 (p. 724) shows that Z-enzyme *per se* is without action on the α-1 : 4-glucosidic links of either amylose or amylopectin. Amylose was then incubated with crystalline β-amylase, alone and in the presence of Z-enzyme or the dilute α-amylase. Measurements of intensity of iodine stain [A.V. (680 mμ)] and reducing power were made after 6 and 19 hours and the results (Table 1) established that the arrest point of action had in each case been reached within 6 hours. It is thus obvious that, while Z-enzyme assists β-amylase in effecting the conversion of more than 90% of amylose into maltose, its action in this respect cannot be distinguished from that of dilute α-amylase. With amylopectin as the substrate in a similar series of experiments, the mixture of β-amylase and Z-enzyme, was, however, sharply differentiated from the mixture of α- and β-amylases (Table 1). It is clear also that the actions on amylopectin of (i) crystalline β-amylase, (ii) a mixture of Z-enzyme and crystalline β-amylase, and (iii) stock soya β-amylase are identical. None of these enzyme combinations brings about a conversion into maltose greater than 52·5%. The mixture of α- and β-amylases, on the other hand, effects a much more substantial hydrolysis of amylopectin, as is to be expected because, by fragmenting the "inner chains," α-amylase exposes new chain-ends to attack by β-amylase. That

Z-enzyme can act on amylose independently of the simultaneous action of β-amylase was shown by the fact that, when amylose was digested with Z-enzyme for 10 hours and the enzyme then destroyed by heat, the subsequent conversion of the amylose into maltose by crystalline β-amylase was 97·7%, compared with the value of 67·5% for the same sample of amylose before treatment with Z-enzyme. In an analogous experiment, in which Z-enzyme was replaced by dilute α-amylase, the subsequent % conversion into maltose effected by the β-amylase was lower, namely, 89·4%. α-Amylase fragments the linear chains of amylose and in acting for a limited period and in high dilution would be expected to yield some chains which were still protected by the anomalous linkages from endwise attack by β-amylase, thus accounting for the lower degree of conversion into maltose.

TABLE 1. *Action of α-amylase, β-amylase, and Z-enzyme on amylose and amylopectin.*

	Amylose, B.V. 1·45				Amylopectin, B.V. 0·158			
	6 hr.		19 hr.		2 hr.		7 hr.	
Enzyme(s)	Convn., %	A.V. (680 mμ)	Convn., %	A.V. (680 mμ)	Convn., %	A.V. (680 mμ)	Convn., %	A.V. (680 mμ)
Z	0·0	1·40	1·3	1·39	0·0	0·158	0·0	0·160
α	1·8	1·37	—	—	3·8	0·106	7·3	0·084
β	67·3	0·357	67·5	0·340	51·2	0·088	51·5	0·088
β + Z	90·5	0·079	93·4	0·038	52·3	0·088	51·5	0·088
β + α	96·0	0·010	—	—	58·3	0·032	64·9	0·023
Stock soya	91·5	0·055	92·0	0·042	50·9	0·095	52·5	0·073

All digests incubated at 35° and pH 4·8. Convn., % = conversion (%) into maltose; β = crystalline sweet-potato β-amylase; Z = Z-enzyme; α = freeze-dried salivary α-amylase; stock soya = stock soya-bean β-amylase.

With whole starch as substrate, the action of purified soya-bean β-amylase, with and without the addition of Z-enzyme, was compared with that of stock soya-bean β-amylase. The results given in Table 2 demonstrate, as in Part XV (p. 705), the different limits of action of purified β-amylase and stock soya-bean β-amylase, and also that when the action of pure soya-bean β-amylase is supplemented by that of Z-enzyme the limit of action of the enzyme mixture is identical with that of stock soya-bean β-amylase. The initial rate of action of the stock preparation is more rapid than that of the mixture, but the difference can be ascribed to a difference of Z/β ratio in the stock soya preparation and in the artificial mixture. The arrest point of action of the soya enzyme or of the mixture on starch, namely, 60% conversion into maltose, is that usually quoted as the hydrolysis limit by "β-amylase" preparations and there is no doubt that this hydrolysis is achieved by the agency of two enzymes. The arrest point of hydrolysis of starch by β-amylase alone is much lower (53%).

TABLE 2. *β-Amylolysis of potato starch* (B.V., 0·425) *in presence of Z-enzyme.*

	β-Amylase		β-Amylase + Z-enzyme		Stock soya-bean β-amylase	
Age of digest (hr.)	Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)
0·5	44·7	0·210	47·6	0·217	54·7	0·104
2·5	53·0	0·174	55·6	0·146	60·0	0·094
8·5	54·0	0·160	59·5	0·110	60·4	0·091
23	—	0·158	62·4	0·094	60·9	0·091
71	56·5	—	61·7	—	—	—

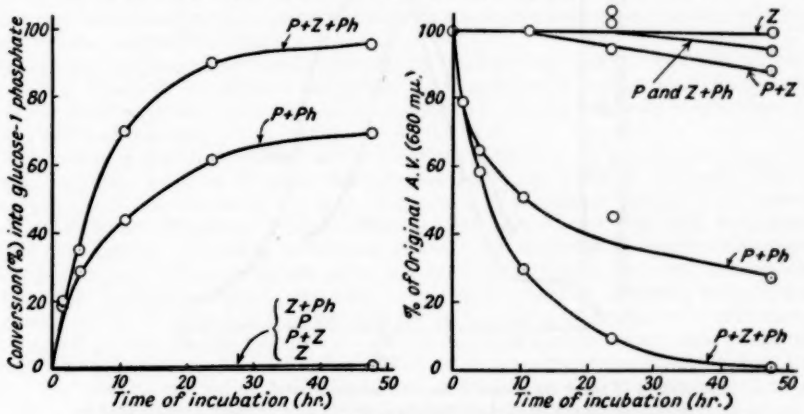
Z-Enzyme and the Phosphorolysis of Starch Polysaccharides.—Since phosphorylase, like β-amylase, degrades starch polysaccharides by an endwise attack on the terminal non-reducing glucose units it is reasonable to suppose that, unless the phosphorylase preparation contains Z-enzyme, phosphorolytic action on amylose should terminate at a limit of conversion similar to that found during the hydrolysis of amylose by pure β-amylase. Hestrin (*J. Biol. Chem.*, 1949, **179**, 943) found that the rate of action of crystalline muscle phosphorylase on maize amylose diminished markedly at a conversion into glucose-1 phosphate of 70%. The effect was ascribed to retrogradation (ageing) of the amylose. It would seem more probable that the incomplete conversion was due to the

absence of Z-enzyme, since it has been shown that Z-labile linkages are present also in maize amylose (Part XVI, preceding paper). Katz and Hassid (*Arch. Biochem.*, 1951, **30**, 272) find that phosphorolysis and arsenolysis of potato amylose by potato phosphorylase lead to substantially complete conversions into glucose-1 phosphate and glucose respectively, the rate curves showing no inflextion at 70% conversion. We cannot confirm this effect with our preparation of potato phosphorylase; its action on potato amylose terminates in the region of 70% (Fig. 1). When, however, Z-enzyme was also present the degree of conversion was 95·4%.

These observations on the effect of Z-enzyme on the phosphoroloysis of amylose parallel those of its effect on β-amylolysis. Furthermore, we have found that Z-enzyme is equally ineffective in extending the limit of conversion of amylopectin by potato phosphorylase or by β-amylase (Table 6, p. 730). It is reasonable to conclude therefore that potato amylose contains in its structure linkages which function as barriers to the progress of both phosphorolysis and β-amylolysis and that these barriers are removed by Z-enzyme.

The Nature of Z-Enzyme Action.—While this work was in progress, Dillon and O'Colla reported that an unfractionated specimen of wheat β-amylase contained an enzyme

FIG. 1. *Effect of Z-enzyme on the phosphorolysis of amylose* (B.V. 1·40).



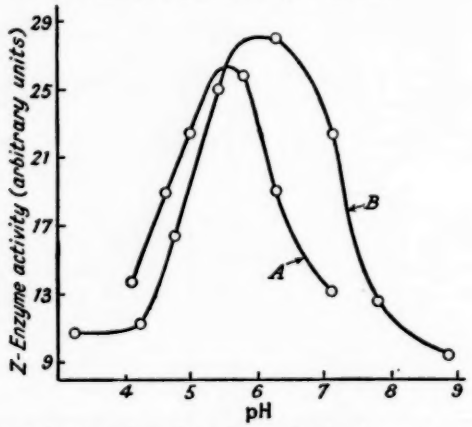
P = Potato phosphorylase; Z = Z-enzyme; Ph = phosphate buffer, pH 6·7.

(laminarinase) which brought about the hydrolysis of laminarin to glucose (*Nature*, 1950, **166**, 67).* Laminarin, a seaweed polysaccharide, is a polyglucose containing β-1 : 3-linkages. We found that a sample of laminarin, kindly presented to us by Professor Dillon, was hydrolysed by stock soya β-amylase (Table 7, p. 730), the limiting yield of glucose (72·3%) agreeing closely with the value of 70% reported by Dillon and O'Colla for the wheat enzyme. Furthermore, pure Z-enzyme also hydrolysed laminarin. There is thus a strong indication that the Z-enzyme of soya bean and the laminarinase of wheat are identical in function. Supporting this view is the fact that the pH optima of the action of pure Z-enzyme on amylose and of the Z-enzyme in the stock soya β-amylase preparation on laminarin are similar (Fig. 2).

The action of Z-enzyme is not, however, confined to β-1 : 3-linkages since it also hydrolyses cellobiose, in which the linkage is β-1 : 4, gentiobiose, with a β-1 : 6-glucosidic link, and the β-1 : 2-linkages of crown gall polysaccharide (Putnam, Potter, Hodgson, and Hassid, *J. Amer. Chem. Soc.*, 1950, **72**, 5024). The only structural feature possessed in common by these polyglucoses is the glucosidic link (or links) which in each case has the β-configuration. It would appear therefore that Z-enzyme is a β-glucosidase, with group, rather than absolute, specificity. Confirmation of this view was forthcoming from the demonstration that the β-glucosidase of almonds (emulsin) could replace Z-enzyme as the factor required to supplement the hydrolysis of amylose by β-amylase (Table 9, p. 731)

and that the presence of emulsin did not influence the degree of β-amylolysis of amylopectin (Table 10, p. 731). Incidentally, Table 10 shows that the emulsin was not contaminated with α-amylase. The probable identity of Z-enzyme and emulsin was further supported by the results of the following experiments. First, emulsin is like Z-enzyme in not being dependent (for its action on amylose) on the presence of β-amylase; amylose, pre-treated with emulsin, was hydrolysed to a greater extent by β-amylase than was untreated amylose (Table 11, p. 731). Secondly, it was shown that mercuric chloride did not inhibit the hydrolysis of cellobiose by emulsin, nor did it inhibit the "debranching" actions of Z-enzyme or emulsin on amylose, as shown by the fact that the limits of phosphorolysis of an amylose treated, in presence of mercuric chloride, with either Z-enzyme or emulsin were 98·9 and 94·0% respectively (Table 12, p. 732). It is to be noted that this experiment sharply distinguishes Z-enzyme and emulsin from the α-1 : 4-glucosidases, α-amylase, β-amylase, and maltase, each of which is completely inhibited by mercuric chloride, and adds further to the evidence already presented that Z-enzyme exerts a true "debranching"

FIG. 2. *Optimum* pH *of Z-enzyme.*



A = Action of stock soya-bean β-amylase on laminarin.
B = Action of Z-enzyme and crystalline β-amylase on amylose limit β-dextrin.

action and is not merely a weakly active α-amylase. Z-Enzyme is also differentiated in this way from R-enzyme which "debranches" amylopectin (Part XIV; *J.*, 1951, 1451) and is inhibited by mercuric chloride. Finally, it was shown that emulsin, like Z-enzyme, hydrolyses laminarin (Table 13, p. 732; cf. Table 7, p. 730).

There is therefore substantial evidence that Z-enzyme is a β-glucosidase, and hence that the Z-labile linkages in potato amylose have the β-configuration. The location of these links in the amylose chains has not yet been determined, but several possible structures are being considered. Z-Enzyme appears to operate by an endwise attack on *terminal* β-glucosidic links inasmuch as paper chromatography of laminarin hydrolysates reveals that glucose is the only product of low molecular weight (cf. Dillon and O'Colla, *Chem. and Ind.*, 1951, 111) and, moreover, the action of Z-enzyme on amylose is independent of the presence of β-amylase. These facts suggest that the Z-labile links in amylose, unlike the branch linkages in amylopectin, join *single* glucose residues to the main chains.

EXPERIMENTAL

Analytical Methods.—All methods used, with the exception of the following, have been detailed in Part XVI of this series (preceding paper).

Determination of total phosphorus content of polysaccharides. The dried polysaccharide (100 mg.), contained in a "Pyrex" boiling-tube (7" × 1¼"), was moistened with a few drops of alcohol. Water (2 ml.) and 6N-sodium hydroxide (1·5 ml.) were added and the poly-

saccharide was dissolved by warming. Perchloric acid (60%; 4 ml.) was added, the tube was covered by a glass bulb, and the solution boiled on an electric hot-plate for 3—4 hours. A few drops of " AnalaR " hydrogen peroxide (100-vol.) were added to complete the combustion and when the solution was colourless the contents of the tube were washed into a 25-ml. standard flask. The phosphorus content was determined by Allen's method (*Biochem. J.*, 1940, **34**, 858). A control determination was carried out by the same method, the polysaccharide being omitted, to determine the phosphate content of the reagents. They were usually found to be completely devoid of phosphate. Results of typical determinations using this method are: P in potato amylose, 0·0086, 0·0085, in potato amylose β-limit dextrin, 0·0359, 0·0317, in maize amylose, 0·0061, 0·0059%.

Preparation of Enzymes.—Stock soya-bean β-amylase was prepared as in Part II (*J.*, 1945, 882), and purified soya β-amylase by the method of Part XVI (preceding paper). Crystalline sweet-potato β-amylase was the gift of Dr. A. K. Balls.

Bone phosphatase was prepared by Martland and Robison's method (*Biochem. J.*, 1929, **23**, 237); by the test described below, it was found to contain α-amylase which was removed by adsorption on starch grains (cf. Part XIV, *J.*, 1951, 1451); the resulting enzyme preparation was completely devoid of α-amylolytic activity but hydrolysed glycerophosphate rapidly. An aqueous solution (450 ml.) of bone phosphatase was prepared from the leg bones of two rabbits according to the above method and to it was added sodium sulphate (5 g.), ethanol (113 ml.), and potato starch (37·5 g.). The mixture was stirred for 24 hours at 2° and the enzyme isolated from the supernatant solution by precipitation with 2 volumes of acetone, washing with acetone, and drying over phosphoric oxide.

Emulsin was prepared from sweet almonds by Tauber's method (*J. Biol. Chem.*, 1932, **99**, 259). When dissolved in water it exhibited maltase activity, but a solution prepared by shaking the enzyme powder in 0·2*M*-acetate buffer (pH 4·8) and removing undissolved protein did not hydrolyse maltose.

Measurement of Enzyme Activity.—(a) *β-Amylase.* See Part XVI (preceding paper).

(b) *α-Amylase.* In order to detect small amounts of α-amylase in the presence of an excess of β-amylase, use was made of the fact that, whereas β-amylase brings about only slight hydrolysis of amylose glycollate (Peat, Bourne, and Thrower, *Nature*, 1947, **159**, 810), α-amylase degrades the amylose glycollate to achroic dextrin. A solution of amylose glycollate was incubated with crystalline α-amylase until the limit of hydrolysis (2—5% conversion) was reached. The resulting solution was used as substrate for the specimen being tested for α-amylase. α-Amylase activity was detected by measurement of fall in A.V. (680 mμ) of the iodine-stained polysaccharide. Under the conditions described below the rate of fall of A.V. (680 mμ) was uniform over an incubation period of 10 hours, and the change taking place in 5 hours was used as the measure of α-amylase activity. In some experiments amylopectin limit β-dextrin was used instead of the glycollate, the behaviour of the two polysaccharides with respect to α- and β-amylases being similar. The digests contained amylose glycollate (7 mg.; 3 ml.), 0·2M-acetate buffer (pH 7·0; 1 ml.), crystalline β-amylase (1000 units; 0·2 ml.), and test solution and water to 11·2 ml. The temperature of incubation was 35°. A portion (1 ml.) of the digest was withdrawn initially, and after 5 hours' incubation, for measurement of A.V. (680 mμ) after staining with standard iodine solution (0·02% in 0·2% KI; 1 ml.) and 6N-sulphuric acid (1 drop) in a total volume of 100 ml.

(c) *Phosphatase.* The optimum pH of soya-bean phosphatase, acting on sodium glycerophosphate, was found to be 5·5. A solution of this pH was prepared by dissolving sodium glycerophosphate (1·25 g.) and 0·2M-acetate buffer (pH 4·8; 30 ml.) in a total volume of 250 ml. The digests used in testing for phosphatase activity contained glycerophosphate solution (18 ml.) and enzyme solution (0·5 ml.). They were incubated at 35° for 45 minutes and then the mineral phosphate content of the digest was determined. Provided that the amount of phosphate liberated was less than 0·08 mg. the relation between degree of hydrolysis and enzyme concentration was linear.

(d) *Z-Enzyme.* The method used was to allow the Z-enzyme to act on amylose limit β-dextrin in the presence of an excess of β-amylase. Removal of the anomalous links in the amylose-dextrin by Z-enzyme enables the β-amylase to bring about further hydrolysis, which was detected by measurement of A.V. (680 mμ) after staining with iodine. The dextrin solution was prepared by dissolving amylose (B.V. 1·40; 110·2 mg.) in 0·1N-sodium hydroxide (50 ml.), neutralising the solution with N-sulphuric acid, and addition of 0·2M-acetate buffer (pH 4·8; 12 ml.), crystalline β-amylase (5000 units; 1 ml.), and water to 100 ml. The solution was incubated at 35° for 6 hours during which the limit of hydrolysis by the β-amylase was reached.

This dextrin solution (15 ml.) and the solution under test (1 ml.) were incubated together for 2 hours at 35°. A portion (2 ml.) was removed for staining with iodine solution (2 ml.) in a total volume of 100 ml. Under these conditions the extent of degradation of the limit dextrin was approximately proportional to the concentration of the enzyme until the A.V. (680 mμ) had decreased by more than 23%.

β-Amylolysis of Amylose treated with Bone Phosphatase.—Two digests were prepared containing amylose solution (B.V. 1·35; 25 mg.; 18·77 ml.), 0·2M-citrate buffer (pH 8·2; 6 ml.), and water to 50 ml. In addition bone-phosphatase solution (52·2 mg.; 13 ml.) was included in one of the digests. Both were incubated at 35° for 23 hours after which time the B.V. of the amylose in each digest was measured, on 2-ml. portions, and found to be unchanged. Both digests were then heated to 100° and, after cooling, the pH was adjusted to 5·2 with citric acid solution. Crystalline β-amylase (2500 units; 0·5 ml.) was added to the digests which were incubated at 35°. Measurements of A.V. (680 mμ) and reducing power were made at intervals as in Table 3.

TABLE 3. *Action of β-amylase on amylose treated with phosphatase.*

	Untreated amylose		Phosphatase-treated amylose	
Age of digest (hrs.)	Conversion into maltose (%)	A.V. (680 mμ)	Conversion into maltose (%)	A.V. (680 mμ)
0·5	61·2	0·382	68·1	0·339
4	67·3	0·359	70·5	0·327
11	71·5	0·346	70·9	0·316
24	72·0	0·334	72·5	0·304

Fractionation of Stock Soya-bean β-Amylase on a Chromatopile.—The apparatus was essentially that described by Mitchell, Gordon, and Haskins (*J. Biol. Chem.*, 1949, **180**, 1071) but the procedure differed in that the ammonium sulphate solution, after passage through the filter papers, was collected in 6-ml. fractions by means of Phillips's automatic collector (*Nature*, 1949, **164**, 545). The lower disc holding the filter papers was constructed of " Perspex," being a hollow cylinder, perforated on the side in contact with the filter paper and channelled inside, the channels leading to a spout from which the solution dripped into the fraction collector. The filter-paper pile was contained within a close-fitting cylinder of " Perspex " to prevent evaporation of solution from the paper.

Stock soya β-amylase (800 mg.) was shaken with water (20 ml.), and the insoluble portion removed on the centrifuge. The supernatant solution was absorbed on 20 sheets of Whatman No. 1 9-cm. filter paper, dried in a desiccator over phosphoric oxide, and the papers were inserted at the top of a pile of 780 papers, covered by a further 20 papers, and clamped in the apparatus. The enzymes were eluted by the concentration-gradient method of the above authors, starting with half-saturated ammonium sulphate (pH 6·5). The fractions were tested for Z-enzyme, phosphatase, and β-amylase activity by the standard methods. In all, 68 fractions (6 ml. each) were collected, Z-enzyme and phosphatase being generally found in the same fractions. β-Amylase was, however, absent and, on dismantling of the chromatopile and elution of the separated sheets, was found to have moved to a position 200 sheets from the lower end, being spread over a thickness of 150 sheets. Some of the eluates containing Z-enzyme and phosphatase were combined and stored in the refrigerator for 2 weeks. After this time Z-enzyme activity had disappeared but the phosphatase activity was still present.

Isolation of Z-Enzyme.—Portions (50 mg.) of stock soya-bean β-amylase were shaken in 0·2M-acetate buffers (25 ml.) of pH 3·0 and pH 4·8, and the insoluble residues removed. The solutions were heated at 35° and at intervals portions were removed for determination of Z-enzyme, α-amylase, β-amylase, and phosphatase activity by the standard methods, the pH of each solution being adjusted to the appropriate value before determination of the enzyme activity. In Table 4 the enzyme activities remaining in the solutions treated at pH 3·0 are expressed as percentages of the activities remaining in the solutions treated at pH 4·8 for the same length of time.

TABLE 4. *Acid* (pH 3·0) *treatment of stock soya-bean β-amylase at* 35°.

	Enzyme activity remaining (%)			
Time of heating (hr.)	Z-Enzyme	α-Amylase	β-Amylase	Phosphatase
1	133	0	3·9	47
2	129	0	—	—
3	95	—	—	—

Z-Enzyme was prepared by shaking stock soya β-amylase (600 mg.) with 0·2M-acetate buffer (pH 3·0; 300 ml.) and removing the insoluble residue on the centrifuge. The solution was kept for 90 minutes at 35°, then cooled, and the pH was adjusted to 4·8 by the addition of N-sodium hydroxide solution. The β-amylase activity had fallen to 0·6% of the original value. The solution was divided into three equal parts, one of which was freeze-dried and to the others were added 2 volumes of methyl alcohol and acetone respectively. The precipitates were centrifuged, washed with the appropriate solvent, and dried in a vacuum over phosphoric oxide. The weights of each preparation were, respectively, 2·37 g., 64·7 mg., and 31·9 mg., the high weight of the freeze-dried preparation being due to its consisting largely of acetate buffer. The units of Z-enzyme activity contained in the three preparations were, respectively, 1997, 769, and 110. It was evident that freeze-drying afforded the best method of isolating Z-enzyme from solution. The freeze-dried preparation was devoid of phosphatase activity. Attempts to modify this procedure by using a greater initial concentration of stock soya β-amylase were unsuccessful. The above method, incorporating the freeze-drying technique, has been used in all subsequent preparations of Z-enzyme.

β-Amylolysis in the Presence of Z-Enzyme or α-Amylase.—The technique used in the β-amylolysis of amylaceous polysaccharides has been described in Parts XV and XVI (preceding papers). In the experiments reported in Tables 1 and 2, the volume of each digest was 25 ml. and the earlier method was modified insofar as 300 units of β-amylase were used in each digest instead of 1300 units. The amounts of Z-enzyme and α-amylase, when present, were 75 mg. and 0·3 mg. respectively. The source of the α-amylase was saliva which had been diluted with an equal volume of water to precipitate mucins, the supernatant liquid being then freeze-dried. When amylose was treated successively with Z-enzyme (or α-amylase) and β-amylase, two identical digests were prepared and incubated at 35°, one of which was used to determine changes in A.V. (680 mμ) and reducing power caused by the Z-enzyme or α-amylase. After 24 hours the second digest was heated at 100° for 3 minutes, then cooled, crystalline β-amylase (300 units; 0·5 ml.) was added, and the incubation continued at 35°.

Phosphorolysis of Amylose and Amylopectin.—Phosphorylase was isolated from potatoes by precipitation and elution of the lead complex as in Part VI (*J.*, 1950, 84). The enzyme was then concentrated by successive fractionations with ammonium sulphate solution (pH 7·0; 50 g./100 ml.); the precipitate was retained which formed between the following limits of salt concentration (g./100 ml.): 25—35, 22—35, 21—35. It was finally freeze-dried in citrate buffer (pH 6·0) as in Part VI. The activity of the preparation was 106 units per g. In the phosphorolysis of amylose (B.V. 1·40) the following solutions were used: amylose (92·0 mg.; 50 ml.), phosphorylase (279 mg.; 13·5 ml.), Z-enzyme (300 mg.; 13·5 ml.), 0·2M-phosphate buffer (pH 6·8), and 0·5M-citrate buffer (pH 6·0). Six digests were prepared as indicated in Table 5 and diluted to 25 ml. with water. Digests 4, 5, and 6 were paired with digests 1, 2, and 3, but the last set contained phosphate buffer in addition. Digests 4, 5, and 6 were used for the detection of α-amylolytic activity in the phosphorylase and Z-enzyme preparations. Fig. 1 shows that α-amylase was absent from both.

TABLE 5.

Digest no.:	1	2	3	4	5	6
	Volume of solution (ml.)					
Amylose	7	7	7	7	7	7
Phosphorylase	3	3	—	3	3	—
Z-Enzyme	—	3	3	—	3	3
Phosphate buffer	8	8	8	—	—	—
Citrate buffer	2	2	2	2	2	2

At intervals portions (2 ml.) of digests 1, 2, and 3 were removed and treated with water (2 ml.) and magnesia reagent [2 ml., containing magnesium chloride (14 g.), ammonium chloride (17 g.), and aqueous ammonia (*d* 0·880; 30 ml.) in 250 ml. of solution]. The precipitated magnesium ammonium phosphate was removed on the centrifuge, and portions of the supernatant liquor (2 ml. each) were used for determination of mineral phosphate present before and after hydrolysis for 7 minutes at 100° in 10% perchloric acid. The difference between these values corresponds to the amount of glucose-1 phosphate formed. Control experiments had shown that glucose-1 phosphate was partly adsorbed by the precipitate, the recovery under the above conditions being 86·6%, and this value was used to correct the experimental data. At the same times, the reducing powers of the solutions were determined by means of the Shaffer–Hartmann reagent (*J. Biol. Chem.*, 1921, **45**, 377) in order to measure the amount of glucose liberated from the

phosphate ester by phosphatase action (see Bailey, Thomas, and Whelan, *Biochem. J.*, 1951, **49**, lvi). The Somogyi reagent (*J. Biol. Chem.*, 1945, **160**, 61) was used in all other determinations of reducing power, but could not be used in this instance because of the presence of the interfering phosphate ion (see Bailey and Whelan, *J.*, 1950, 3573). The amounts of glucose, calculated from reducing power, were assumed to be derived from glucose-1 phosphate and were incorporated in the values representing conversion of the polysaccharide by phosphorylase (Fig. 1). The phosphatase action was slight; in 47·75 hours 1·3% and 3·2% of the polysaccharide was present as glucose in digests 1 and 2 respectively. The changes in iodine stain were determined by treating portions (0·97 ml. $\equiv$ 0·5 mg. of amylose) of the digests with standard iodine solution (0·5 ml.) in 50 ml. of solution containing one drop of 6N-hydrochloric acid, and measuring the A.V. (680 mμ). These concentrations correspond to the standard conditions of A.V. determination used throughout this series.

The phosphorolysis of amylopectin in the presence and in the absence of Z-enzyme was carried out in the same manner, and the numbered digests in Table 6 were of the same composition as the corresponding digests in Table 5 above, amylopectin being substituted for amylose.

TABLE 6. *Phosphorolysis of amylopectin* (B.V., 0·184) *in the presence and the absence of Z-enzyme.*

Digest no.:	1		2		3		4	5	6
Age of digest (hr.)	Conv.,* %	A.V. (680 mμ)	Conv., %	A.V. (680 mμ)	Conv., %	A.V. (680 mμ)	A.V. (680 mμ)	A.V. (680 mμ)	A.V. (680 mμ)
1·5	37·6	0·108	39·5	0·116	0·2	0·184	0·198	0·184	0·185
5·5	45·7	0·102	48·3	0·102	—	0·164	0·172	0·176	0·163
24·25	48·3	0·103	47·1	0·102	—	0·169	0·176	0·175	0·162

* Conv., % = Conversion (%) into glucose-1 phosphate.

It will be noticed that the limiting conversion of the amylopectin into glucose-1 phosphate, namely, 48%, is higher than the previously reported value of 39% (Part III, *J.*, 1949, 1448). The latter agrees with the findings of other workers. The degree of β-amylolysis of the amylopectin (58·8%) was also correspondingly higher than the normal value of 51·5%. This specimen was a sub-fraction of potato amylopectin purified as in Part XIII (*J.*, 1951, 801) and it possesses unusual properties, the significance of which will be discussed in a later paper. The abnormality of the specimen in no way affects the conclusions concerning the lack of action of Z-enzyme on amylopectin.

Action of Stock Soya-bean β-Amylase on Laminarin.—A digest containing laminarin solution (29·9 mg.; 20 ml.), stock soya β-amylase solution (238 mg.; 20 ml.), and water (10 ml.) was incubated at 35° and measurements of reducing power (as glucose) were made at intervals. A control digest without the laminarin was incubated at the same time to determine the reducing power of the enzyme preparation. The results are given in Table 7. After incubation for 175 hours, fresh enzyme solution, containing 150 mg. of enzyme, was added to each digest. No further hydrolysis took place. Similar digests were incubated in which stock soya β-amylase was replaced by crystalline β-amylase in equivalent amount or by freeze-dried salivary α-amylase (2·0 mg.; see above). In neither case did hydrolysis take place during 36 hours.

TABLE 7. *Action of stock soya-bean β-amylase on laminarin.*

Age of digest (hr.)	3	20	44	68	99	142	167
Conversion into glucose (%)	5·9	29·4	47·0	56·5	67·1	72·3	72·3

Action of Z-Enzyme on Laminarin, Cellobiose, and Gentiobiose.—Three digests containing Z-enzyme solution (600 mg.; 5 ml.), with laminarin, cellobiose, or gentiobiose (5 mg. each) in a total volume of 10 ml. were incubated at 35° for 146 hours, whereafter a further quantity of Z-enzyme solution (4·5 ml.; 407 mg.) was added to each digest. After a further 54 hours portions of the digests (1·5 ml.) were removed and after deproteinisation the reducing powers were determined. The conversions of the above substances into glucose were found to be 23·2, 5·3, and 35·4% respectively.

Effect of Z-Enzyme and Emulsin on the Hydrolysis of Amylose by β-Amylase.—The following solutions were used to prepare the digests shown in Table 8. Amylose (B.V. 1·40; 100 mg.; 50 ml.), 0·2M-acetate buffer (pH 4·8), Z-enzyme (152·4 mg.; 7 ml.), emulsin [401 mg. in 0·06M-acetate buffer (pH 4·8; 10 ml.)], and purified soya β-amylase (900 units/ml.). All digests were diluted with water to 25 ml. and incubated at 35°. At intervals, portions (2 ml.) were removed

for determination of reducing power and further portions (1 ml.) for determination of A.V. (680 mμ) under the standard conditions (see Table 9). Digest no. 4 was used for determination of the reducing power of the emulsin preparation.

TABLE 8.

Digest no.	Volume of solution (ml.) Amylose	Buffer	Z-Enzyme	Emulsin	β-Amylase
1	6·25	3	3	—	0·5
2	6·25	2	—	3	0·5
3	6·25	2	3	3	0·5
4	—	2	—	3	0·5

TABLE 9. *Effect of Z-enzyme and emulsin on the β-amylolysis of amylose.*

Age of digest (hr.)	Z-Enzyme (digest no. 1) Conversion into maltose, %	A.V. (680 mμ)	Emulsin (digest no. 2) Conversion into maltose, %	A.V. (680 mμ)	Z-Enzyme + emulsin (digest no. 3) Conversion into maltose, %	A.V. (680 mμ)
1	71·9	0·305	86·4	0·117	88·8	0·086
3	83·0	0·185	89·5	0·056	—	—
5·75	87·0	0·117	90·8	0·055	93·5	0·044
11·3	92·8	0·067	93·3	0·060	92·6	0·049
22·75	94·6	0·057	93·7	0·055	94·6	0·045

Effect of Emulsin on the β-Amylolysis of Amylopectin.—Two digests were prepared corresponding to nos. 2 and 4 in Table 8, and a third digest similar to no. 2 but containing 0·06M-acetate buffer (pH 4·8; 3 ml.) instead of emulsin solution. In each digest amylopectin (B.V. 0·196) replaced amylose. All digests were treated as above and the results of the experiment are given in Table 10.

TABLE 10. *Effect of emulsin on the β-amylolysis of amylopectin.*

Age of digest (hr.)	Emulsin + β-amylase Conversion into maltose, %	A.V. (680 mμ)	β-Amylase Conversion into maltose, %	A.V. (680 mμ)
1·5	47·6	0·118	50·7	0·124
4	48·9	0·118	51·9	0·119
11·5	49·7	—	51·6	0·119
24·75	51·3	0·120	—	—

β-Amylolysis of Emulsin-treated Amylose.—Amylose solution (B.V. 1·40; 25·05 mg.; 12·5 ml.), emulsin solution (92·7 mg.; 3 ml., prepared as above), and water (25 ml.) were mixed and incubated at 35° for 23·5 hours. After this time the B.V. of the amylose had fallen to 1·26, probably owing to partial precipitation of the iodine complex caused by the presence of emulsin protein. No visible retrogradation of amylose occurred in the digest. A similar digest, containing buffer

TABLE 11. *β-Amylolysis of emulsin-treated amylose.*

Age of digest (hr.)	Untreated amylose Conversion into maltose, %	A.V. (680 mμ)	Emulsin-treated amylose Conversion into maltose, %	A.V. (680 mμ)
0·5	59·8	0·397	—	—
1	67·7	0·368	79·5	0·173
3	70·0	—	82·2	0·150
5·5	72·0	0·313	—	—
22·5	72·5	—	86·3	0·142

instead of emulsin solution, was also incubated for 23·5 hours. Both digests were heated at 100° for 10 minutes, then cooled, and portions (15 ml.) removed and treated with purified soya β-amylase (500 units; 0·3 ml.) at 35°. Measurements of reducing power and A.V. (680 mμ) were made as in the previous experiment (see Table 11).

Action of Z-Enzyme in Presence of Mercuric Chloride.—Two digests were prepared containing the following solutions: amylose (B.V. 1·40; 8·86 mg.; 10 ml.), 0·5M-citrate buffer (pH 6·0; 1 ml.), and 0·000154M-mercuric chloride (0·14 ml.). In addition one digest contained Z-enzyme solution (50 mg.; 2·5 ml.). Both digests were diluted to 14·14 ml. and incubated for 32·5

hours at 35°. They were heated at 100° for 10 minutes, then cooled, and the following solutions were added: phosphorylase (9 units; 3 ml.), 0·2M-phosphate buffer (pH 6·8; 7 ml.), and water to 25 ml. Incubation at 35° was then continued, and A.V. (680 mμ) and conversion into glucose-1 phosphate were determined as in earlier experiments. After 39·5 hours, when the arrest points of action had been reached, the A.V. (680 mμ) of the Z-treated amylose was 7·5% of the original value and the conversion into glucose-1 phosphate was 98·9%. The corresponding values for the untreated amylose were 32·0% and 73·4%. It follows that Z-enzyme is not inhibited by mercuric ion.

Effect of Mercuric Chloride on Emulsin.—Two digests of total volume 8·1 ml. were prepared, containing cellobiose (8·1 mg.) and emulsin solution (1·5 ml.), and were incubated at 35°. In addition one digest contained 0·000154M-mercuric chloride (0·08 ml.). The emulsin solution was prepared by dissolving the enzyme powder (300 mg.) in 0·083M-citrate buffer (pH 6·0; 6 ml.) and removing undissolved protein on the centrifuge. Portions (1 ml.) of the digests were used in the measurement of reducing power. In the absence of mercuric chloride the conversions of cellubiose into glucose after 4 and 21·75 hours were 35·6 and 45·4% respectively. In the presence of mercuric chloride the corresponding values were 36·5 and 55·8%. It is concluded that emulsin is not inhibited by mercury.

Effect of Emulsin on the Phosphorolysis of Amylose in the Presence of Mercuric Chloride.—The digest contained the following solutions: amylose (14 mg.; 7 ml.), 0·2M-phosphate buffer (pH 6·8; 8 ml.), phosphorylase (4 units; 1·2 ml.), emulsin (173 mg.; 4 ml.), 0·000154M-mercuric chloride (0·2 ml.), 0·5M-citrate buffer (1 ml.), and water to 25 ml. The temperature of incubation was 35° and after 34 hours a portion (15 ml.) of the digest was removed and mixed with fresh phosphorylase solution (4 units; 1·2 ml.). Measurements were made as before and the results, given in Table 12, confirm that emulsin is not inhibited by mercury and that it has no effect on the phosphorolysis of amylose.

TABLE 12. *Action of emulsin and phosphorylase on amylose in presence of mercuric chloride.*

Age of digest (hr.)	Conversion into glucose-1 phosphate (%)	% of original A.V. (680 mμ)
3·5	37·3	51·0
8·75	59·1	36·2
23·75	65·6	25·5
34	More phosphorylase added	—
48	94·0	7·7

Action of Emulsin on Laminarin.—The digest contained laminarin (25·2 mg.) and emulsin solution (320 mg.; 4 ml.) in a total volume of 25 ml. The temperature of incubation was 35°. and portions (1 ml.) were removed at intervals for measurement of reducing power as glucose (Table 13). A second digest, containing only emulsin solution, was used to determine the reducing power of the enzyme.

TABLE 13. *Hydrolysis of laminarin by emulsin.*

Age of digest (hr.)	3·75	19·25	44·75	123	167	263	331	527	1103
Conversion into glucose (%) ...	2·4	3·6	6·2	15·8	18·2	28·7	36·1	50·4	72·8

Optimum pH *of Z-Enzyme.*—Amylose (B.V. 1·40; 109·2 mg.) was dissolved in 0·3N-sodium hydroxide (20 ml.), and neutralised with 6N-sulphuric acid. 0·2M-Acetate buffer (pH 4·8; 0·1 ml.) and crystalline β-amylase (1000 units; 1 ml.) were added and the solution was diluted to 100 ml. The digest was incubated at 35° for 2 days and the resulting solution of amylose β-limit dextrin was used in the determination of Z-enzyme activity as described above. The activity was determined at eight different values of pH, which was controlled by the use of 0·13N-sodium veronal buffer (see Fig. 2).

Optimum pH *of Hydrolysis of Laminarin.*—Stock soya-bean β-amylase (315·3 mg.) was shaken with water (30 ml.) and filtered. To portions (3 ml.) of the solution were added portions (3 ml.) of 0·13M-sodium veronal buffer of various hydrogen-ion concentrations. The enzyme buffer mixtures (5 ml.) were incorporated in digests containing laminarin solution (7·47 mg.; 3·75 ml.) and water (3·75 ml.), which were incubated at 35°. After 67·5 hours the reducing power (after deproteinisation) and pH of each digest were determined (see Fig. 2).

Action of Z-Enzyme on Crown-gall Polysaccharide.—The polysaccharide (7·7 mg.) was dissolved in warm water (10 ml.). Z-Enzyme solution (500 mg.; 5 ml.), 0·2M-acetate buffer (pH 4·8; 3 ml.), and water to 25 ml. were added, and the digest was incubated at 35°. After

166 hours the degree of conversion into glucose was 7·4%, and after 185 hours was 8·0%. These figures should be compared with those given earlier for the action of Z-enzyme on laminarin, cellobiose, and gentiobiose.

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131. *The Comparative Ease of Oxidation of Various Ethers in the Gaseous Phase.*

By T. A. EASTWOOD and SIR CYRIL HINSHELWOOD.

A comparative study has been made of the reactions of a series of ethers with gaseous oxygen. In the low-temperature region of slow reaction the kinetics are generally similar for the various members, which also resemble certain hydrocarbons in that the rate passes through a maximum with increasing oxygen concentration. This rate is linearly (or less) dependent on the ether concentration. In these respects the ethers can be regarded as substituted hydrocarbons and included in a general structural survey. Quantities of peroxides (much larger than with hydrocarbons) are formed and reach a maximum at the same time as the rate of pressure increase. Cool flames appear in certain regions of pressure and temperature. The general position of the areas of cool flame, ignition, and slow reaction has been mapped for the series of ethers. In sharp contrast with what occurs in the oxidation of butanone the peroxide concentration shows little change during the passage of a cool flame. The role and possibly the nature of the peroxides present in the two cases appear to be different.

The introduction of the ethereal oxygen leads to a very great enhancement of reactivity, and though the methyl group, as in hydrocarbons, remains resistant to attack, the response of the oxidation rate to increase in the length of the alkyl chain is subject to a marked saturation effect, there being no increase beyond diethyl ether—in contrast with what is observed in the normal paraffin series. The nature of the structural influence is discussed in terms of an electron attractive ($-I$) effect of OR groups.

LOW-TEMPERATURE reactions of gaseous oxygen with hydrocarbons and their derivatives present many features of interest, and this paper continues the study of the effect of structure and substitution on the various phenomena associated with the oxidation. It deals with the homologous series of the ethers. First, the general kinetic relations are examined for comparison with the hydrocarbon series. Then the role of peroxides in the slow reaction and in the cool flames is considered, and finally a comparison of reactivity throughout the series is made.

EXPERIMENTAL METHODS AND RESULTS

Ether vapour and oxygen were admitted separately to a " Pyrex " reaction vessel of 250 ml. capacity and of diameter approximately 8 cm., kept at constant temperature, and the reaction was followed by observation of the pressure change and by peroxide analyses. The details were as previously described (Cullis and Hinshelwood, *Discuss. Faraday Soc.*, 1947, **2**, 117; Cullis and Smith, *Trans. Faraday Soc.*, 1950, **46**, 42). Peroxides were usually estimated by the ferrous thiocyanate method but auxiliary analyses were made with potassium iodide in neutral and acid solutions. An initial pressure decrease of some magnitude was observed during the slow combustion of the ethers but was eventually followed by the normal pressure

increase. The maximum rate of pressure increase ($\rho_{max.}$) was taken as a measure of the rate of reaction.

Kinetic Characteristics of the Slow Reaction.—All the ethers studied were found to be generally similar in the kinetics of their slow oxidation, the results with diethyl ether, given below, being typical.

(1) *Oxygen pressure.* The dependence of the maximum rate on the oxygen pressure for a constant diethyl ether pressure of 150 mm. at several temperatures is shown in Fig. 1. It is seen that the rate first rises with increasing oxygen pressure but ultimately falls to low values. The curve for 173° is necessarily incomplete since ether-rich mixtures give rise to cool flames (characterised by a rapid increase in pressure and a final pressure increase of less than 50%)

FIG. 1. *The effect of oxygen pressure on the maximum rate of oxidation of diethyl ether at 150 mm. pressure. Temperatures; 173°, 168°, 167°, 162°, 157° in descending order of curves.*

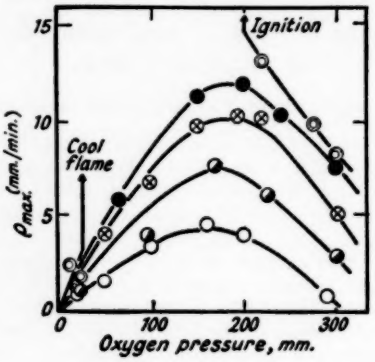

FIG. 2.

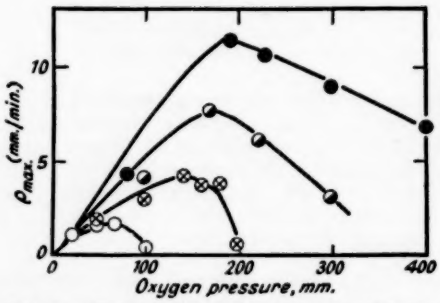

FIG. 3.

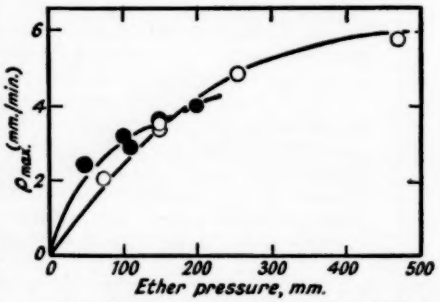

FIG. 2. *The variation of the maximum oxidation rate with initial oxygen pressure at 162°. Diethyl ether pressures; 50, 100, 150, 200 mm. in ascending order of curves.*

FIG. 3. *The variation of maximum oxidation rate with diethyl ether pressure at 157°. Oxygen pressures: 50 mm., open circles; 100 mm., filled-in circles.*

while oxygen-rich mixtures give more violent ignitions (rapid pressure increase and a final pressure increase of more than 50%) with the formation of carbon.

The $\rho_{max.}$–oxygen pressure relationship was found to be of the same form for various fixed ether concentrations ranging from 50 to 200 mm. at 162° (Fig. 2).

(2) *Ether pressure.* Fig. 3 shows how the rate increases with an increase in ether pressure, the apparent order of reaction being less than unity. Slightly lower ether–oxygen ratios were used with some of the other ethers, and the dependence was found to be linear. (The range of concentrations over which measurements can be made is restricted by the strong inhibiting influence of oxygen in oxygen-rich mixtures.)

(3) *Temperature.* With 50 mm. of diethyl ether and 50 mm. of oxygen the rate becomes appreciable at about 160° and increases steadily with increasing temperature (Fig. 4). Above 171° the reaction becomes explosive.

Ether combustion, in common with gas-phase oxidations generally, was found to be very sensitive to surface conditions and to deviations from the established experimental procedure. Nevertheless, the results of three groups of experiments with diethyl ether (Fig. 4) made at intervals in the course of over 600 experiments and involving explosions as well as slow reactions, show that reasonable reproducibility can be achieved by rigid standardization of the experimental technique.

To place the results in Fig. 4, and similar results with other ethers, in their proper perspective in the complete range of oxidation behaviour of the various ethers the temperatures at which slow reactions, cool flames, and ignitions occur in equimolar ether–oxygen mixtures were determined over a wide range of pressures. The resulting pressure–temperature explosion diagrams are compared in Fig. 5. Similar diagrams for some of the ethers have been published (Malherbe and Walsh, *Trans. Faraday Soc.*, 1950, **46**, 835, give a summary of the available results) but since they were obtained by different workers under different reaction conditions they are not immediately suitable for a comparative survey. In the region between the upright

FIG. 4.

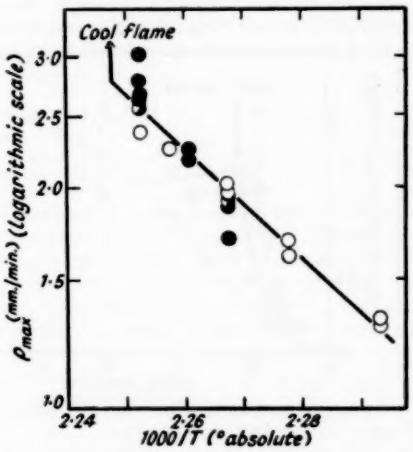

FIG. 5.

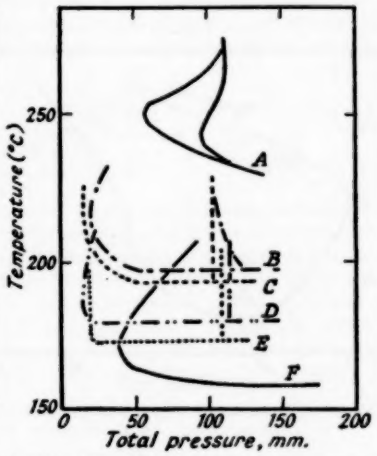

FIG. 4. *The effect of temperature on the maximum rate of oxidation of diethyl ether; ether pressure 50 mm., oxygen pressure 50 mm. Experiments in Groups 1, 2, and 3 shown by different kinds of circle.*

FIG. 5. *The pressure–temperature explosion diagrams for equimolar ether–oxygen mixtures.*

A. Dimethyl ether. *B. Methyl n-propyl ether.* *C. Ethyl methyl ether.*
D. Di-n-propyl ether. *E. Diethyl ether.* *F. Diisopropyl ether.*

boundary lines in Fig. 5 (or in the completely enclosed area of the dimethyl ether diagram) combustion is accompanied by a cool flame. In the area beyond the right-hand boundary, that is at higher total pressures but in about the same temperature range, ignition occurs, while in the area beyond the left-hand boundary slow reaction is observed. As the temperature is lowered from the cool flame or ignition region a boundary is crossed below which slow reactions prevail. Diisopropyl ether was exceptional in that slow reactions and ignitions were not observed at all over a wide range where cool flames or negligible reaction occurred. A complete chart was made with dimethyl ether, and it was found that as the temperature is raised from the cool flame region slow reactions are encountered over a range of pressures, but that a further increase in temperature or an increase in pressure leads to conditions which favour ignition. With the other ethers it was not possible to extend the diagrams to high temperatures because the cool flame or ignition set in so rapidly that the products expanded into the connecting tubes before the oxygen could be completely added to the reaction mixture. Nevertheless, these diagrams demarcate the "low temperature" reaction regions, which are the areas of primary interest in the present survey, and show that the results in Fig. 4 and similar results for other ethers, to be considered in a later section, were obtained under comparable reaction conditions in the low-temperature region.

(4) *Inert gas.* Additions of nitrogen to various mixtures of diethyl ether and oxygen at 168° were found to have no significant influence on the oxidation.

(5) *Peroxide formation.* In the early stages of the reaction much larger quantities of peroxides were detected in the slow combustion of the ethers than with the hydrocarbons. In agreement, however, with observations on the paraffins, chloroparaffins, amines, and ketones, the *maximum* peroxide concentration is not reached until the pressure increase also reaches its maximum (Fig. 6). Corresponding to this large accumulation of peroxide there is initially a diminution of pressure, which is transformed into an increase only when the peroxide has reached its maximum so that its breakdown balances its formation.

In view of the general similarity of the ethers and the other organic compounds previously studied in the kinetics of their low-temperature, slow oxidation, the ethers can be regarded as substituted hydrocarbons and included in a general structural survey.

Role of Peroxides in the Cool-flame Reaction.—The variation in peroxide concentration during the cool-flame reaction of diethyl ether at 172° and 174° is compared with the formation of peroxides in the slow reaction at 170° in Fig. 7. In the cool-flame reaction the peroxide concentration is seen to increase rapidly until the cool flame appears, and thereafter to decrease very slowly.

FIG. 6.

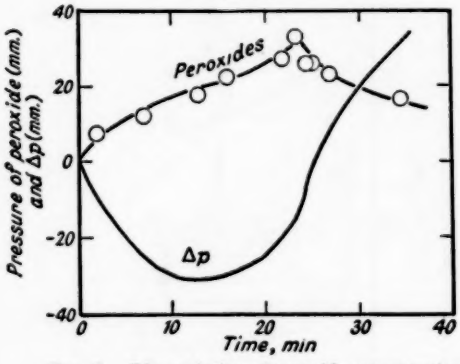

FIG. 7.

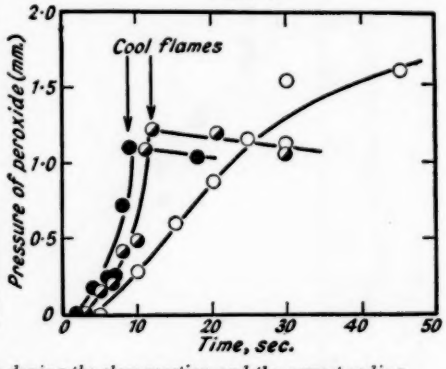

FIG. 6. *The variation of peroxide concentration during the slow reaction and the corresponding* Δp*–time curve. Ether pressure,* 150 *mm.; oxygen pressure,* 250 *mm.*

FIG. 7. *Comparison of the formation of peroxides in the slow and cool-flame reactions, respectively, of diethyl ether. Ether pressure,* 30 *mm.; oxygen pressure,* 30 *mm. Slow reaction at* 170°, *open circles; cool-flame reaction at* 172°, *half-shaded circles; at* 174° *filled-in circles.*

The stability of peroxides during the passage of the cool flame of diethyl ether contrasts strongly with the precipitous decline in the peroxide concentration during the butanone cool flame (Bardwell and Hinshelwood, *Proc. Roy. Soc.*, 1951, *A*, **205**, 375). The behaviour of peroxides in the diethyl ether cool-flame reaction was, therefore, investigated further. A large number of additional analyses of the reaction mixture in the last moment before the appearance of the cool flame confirm the results in Fig. 7 and show that it is unlikely that the concentration of peroxides ever exceeds the values recorded in the figure. It was found, moreover, that a mixture of 30 mm. of ether and 30 mm. of oxygen initially at 170° (*i.e.* in the region of slow reaction) could be heated to 198°, 27° above the lowest temperature at which cool flames appear, without the appearance of a cool flame even though the peroxide concentration was determined to be 2·9 mm. In a similar experiment more oxygen and ether were added separately to the reaction mixture after the temperature had been raised above the cool-flame temperature and again no cool flame appeared. The final temperature was 184° and the peroxide pressure was 3·5 mm. Since peroxides as a whole survive the passage of the cool flame of diethyl ether and, indeed, exist in concentrations above the maximum reached in a cool-flame reaction at temperatures higher than the minimum cool-flame temperature, it would appear that with diethyl ether they do not play the important role in the cool-flame reaction that they do with butanone. There still remains the possibility that a reactive type of peroxide, present in such small amounts relative to the total peroxide concentration that variations in its concentration are not detected, is responsible for the cool flame. Analyses by the methods involving acid or neutral potassium

iodide reveal the same general picture of peroxide formation, so a decision on this matter is not at the moment possible.

Comparison of Reactivity.—In order to compare the reactivities of the ethers and the paraffins a link between the two was established by confirming the results of the slow oxidation of *n*-pentane (Cullis and Hinshelwood, *loc. cit.*) in the present apparatus. It was found that the difference between the reactivities of pentane and the ethers, and often between adjacent members of the ether series also, was so great that the rates could not be conveniently measured at the same temperature. It was usually necessary, therefore, to compare extrapolated values of the rate obtained from log $p_{max.}$–$1/T$ plots, similar to Fig. 4, for the appropriate compounds. The comparisons were made at the same pressure with equimolar mixtures of the organic reactant and oxygen, and the results are summarized in the table. With diethyl and di-*n*-propyl ethers, which can be compared directly at the same temperature, the relative rates depend on the ether–oxygen pressure ratio but the variation does not alter the position of these compounds in the table. Thus the order in which the compounds appear there probably applies over a fairly wide range of reaction conditions in the low-temperature region, although the actual figures may be subject to minor variations. The log $p_{max.}$–$1/T$ relation was not determined for di*iso*propyl ether since, as previously mentioned, the combustion of this compound is extremely slow in the slow-reaction region. A direct comparison, however, of the rates of reaction of 20 mm. of ether and 20 mm. of oxygen at 170° shows that di*iso*propyl ether oxidizes much less readily than diethyl ether.

Compound	Relative rate		Compound	Relative rate	
Pentane	1	—	Methyl *n*-propyl ether	175	7
Dimethyl ether	25	1	Diethyl ether	2500	100
Ethyl methyl ether	175	7	Di-*n*-propyl ether	1300	50

It is clear in the first place that the introduction of –O– into a carbon skeleton leads to a very great enhancement of the reactivity. In the second place it is of interest to observe that the influence of the ethereal oxygen is not reinforced by the lengthening of the carbon chain beyond diethyl ether, in contrast with the progressive increase in the rate of oxidation which occurs on ascent of the paraffin series. It would thus appear that the response of the oxidation rate to enhancement by substitutional influences is subject to a marked saturation effect. The stability of dimethyl and di*iso*propyl ethers emphasises once more the resistance of the methyl group to oxidative attack, a factor already prominent in the low-temperature oxidation of other series of organic compounds.

Discussion of Structural Influences

The two major influences of structure on oxidation are (1) the great tendency for methyl groups to resist oxidation and (2) the influence of electron displacements on the chain-initiating and the chain-branching steps of the total sequence of reactions. This sequence is probably of the general form :

$$RH + O_2 \longrightarrow R^- + HOO^- \text{ (chain-initiating step)}$$
$$R^- + O_2 \longrightarrow ROO^-$$
$$ROO^- + RH \longrightarrow ROOR$$
$$ROOR \longrightarrow 2\ RO^- \text{ (chain-branching step)}$$

While any step may respond to structural changes, the influence of electron displacements on the branching process is likely to be the most important since the effect on this step is magnified by the peculiar kinetics of the low-temperature oxidation reaction. In any case the effects of substitution are likely to be in the same direction in both the chain-initiating and chain-branching steps and so tend to reinforce one another (*Discuss. Faraday Soc.*, 1951, **10**, 266).

It appears in general that the influence of electron displacements on the branching step can be interpreted in terms of a stabilization of the –O–O– linkage in the peroxide by substituents which favour electron accession to the seat of reaction (*i.e.* by substituents with an inductive action represented by $+I$) and a weakening of the peroxide bond by $-I$ substituents. For example, methyl, which is electron-repelling, reduces the oxidation

rate. The relative ease of ether oxidation compared with pentane suggests that the –O–O– linkage in peroxides derived from ethers must be comparatively weak, and thus, according to the rule mentioned, implies that the RO group (an ether being regarded as a hydrocarbon with an RO-substituent) is exerting a $-I$ inductive action. This implication is in agreement with the usual view about the inductive action of the CH_3O group.

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NOTES.

132. *The Periodate Oxidation of Pinitol.*

By ALISTAIR M. STEPHEN.

FORMULATION of sequoyitol by Riggs (*J.*, 1949, 3199) as the 2- rather than the 5-methyl ether of *meso*inositol (of configuration 1235/46 *) rests upon the observed liberation of less than four equivalents of strong acid per mole of sequoyitol on oxidation with neutral sodium metaperiodate. It is suggested that the course of the oxidation is similar to that of *meso*-inositol itself (Fleury, Poirot, and Fievet, *Compt. rend.*, 1945, **220**, 664) in that the initial splitting of the molecule takes place at two points giving two 3-carbon fragments. *cis*-α-Glycol groups are considered to be absent from sequoyitol because such groups would be expected to react first, so rendering the formation of tartrondialdehyde (from which no more than two equivalents of acid could be formed) impossible. According to the mechanism given by Riggs, the amount of acid liberated is in close agreement with that expected from the measured periodate uptake at the 24-hour stage.

The configuration of (+)-inositol (125/346), on the other hand, is such that the behaviour of its monomethyl ether pinitol towards periodate cannot be used to derive a favoured structure for pinitol. On the assumption that *cis*-α-glycol groups react first and Fleury *et al.*'s mechanism operates where possible, a methoxyl group on $C_{(1)}$ or $C_{(4)}$ would cause liberation of more than four equivalents of strong acid, whereas a methoxyl group on $C_{(2)}$ or $C_{(3)}$ would result in less than four equivalents, during the uptake of anything over 6 moles of periodate. With the methoxyl group on $C_{(5)}$ or $C_{(6)}$ two *cis*-α-glycol systems remain and the situation is confused. It is nevertheless of interest that the reaction of pinitol with sodium metaperiodate (at 26°) resembles very closely the oxidation of the isomeric sequoyitol, recorded by Riggs, with respect to periodate consumption and acid production. The initial rapid reaction is followed by a slow increase in the amount of periodate consumed to a value of 6·21 moles per mole of pinitol (at 25 hours) during which time strong acid is produced to the extent of 3·71 equivalents per mole. It would seem, therefore, that $C_{(1)}$ or $C_{(4)}$ is the least likely site for the methoxyl group. Further experiment shows, however, that under different conditions the acid liberated may exceed 4 equivalents per mole: if pinitol is kept for longer than one week or is heated with neutral periodate on a boiling water-bath for 20—40 minutes (cf. Hirst and Jones, *J.*, 1949, 1659) the value averages 3·96 and may rise to as much as 4·16 equivalents per mole. The mechanism of oxidation is no doubt different at the elevated temperature, and sequoyitol might yield considerably more acid under the appropriate conditions. At all events it is certain that conclusions about structure based on measurements of this kind should be treated with the greatest reserve.

Comparison of the oxidation at room temperature of (+)-inositol and *meso*inositol shows

* This representation, rather than $^{1}_{4}2^{3}_{6}5$, is used to economise space.—ED.

that these isomers behave identically, the total periodate uptake (6·74 moles per mole after 25 hours at 26°) being in close agreement with the value (6·7, in 2—3 days) found by Fleury *et al.* (*loc. cit.*). The acid liberated (*ca.* 5·2 equivalents per mole) is, however, considerably in excess of the theoretical as given by these authors (cf. Hirst and Jones, *loc. cit.*); it is not increased by heating.

Experimental.—The pinitol used was isolated from an acetone extract of the timber of *Acacia mollissima* Willd.(cf. Stephen, *J. Sci. Food Agric.*, in the press). It had m. p. 184—186°, undepressed by a sample from *Lotononis laxa* kindly supplied by Professor H. L. de Waal (Found: C, 43·3; H, 7·4; OMe, 15·7. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; 1OMe, 16·0%), and $[\alpha]_D^{26}$ + 62° (*c*, 2·06 in water). The characteristic penta-acetate, m. p. 96—98° after recrystallisation from ethyl acetate–*iso*hexane, had $[\alpha]_D^{28}$ + 6·6° (*c*, 2·12 in ethanol) (lit., m. p. 98°, $[\alpha]_D^{25}$ + 8·6°). From pinitol was prepared (+)-inositol, m. p. 244°, $[\alpha]_D^{28}$ + 66·2° (*c*, 1·21 in water), by hydriodic acid demethylation. *meso*Inositol (m. p. 220°; hexa-acetate, m. p. 215—216°) was obtained by recrystallisation of a commercial sample.

Samples dried at 100° *in vacuo* were made up to 0·01M-strength with aqueous sodium metaperiodate (0·18M.; 50 c.c.) and water (to 100 c.c.), and the residual periodate was measured by the usual arsenite method at various time intervals; room temperature was 26°. The uptake of periodate in moles/mole was:

Time (min.)	5	12	27	45	62	160	300	1500
Pinitol	3·84	4·37	4·79	5·07	5·17	5·59	5·66	6·21
(+)-Inositol	5·46	5·76	6·14	6·38	6·50	6·55	6·60	6·75
*meso*Inositol	4·80	5·55	6·14	6·38	6·50	6·62	6·70	6·74

The small differences in periodate consumption by pinitol and sequoyitol (5·66 and 5·46 moles after 5·8 hours; 6·20 and 5·81 after 24 hours respectively) may be attributed to dissimilarity of experimental conditions, especially temperature.

The following table shows the quantity of strong acid (in equivalents per mole) liberated from these cyclitols at different times. Concentrations and temperature were the same as for the measurement of periodate uptake, and excess of sodium metaperiodate was destroyed before titration with alkali hydroxide (using methyl-red).

Time (min.)	5	10	25	40	80	120
Pinitol	1·68	2·15	2·50	2·73	3·19	3·40
(+)-Inositol	3·89	4·55	4·98	5·10	5·28	5·28
*meso*Inositol	3·70	4·30	4·95	5·07	5·12	5·16

Separate experiments in which the three cyclitols were warmed on the boiling water-bath for 20—40 minutes showed the acid liberated to be 3·95, 5·18, 5·16 equivalents per mole respectively (Hirst and Jones, *loc. cit.*, record 4·32 to 4·56 for *meso*inositol).

From further experiments with pinitol and *meso*inositol it became clear that oxidation at room temperature (in this case 18°) in the dark for times greatly in excess of 24 hours caused practically no change in the amount of acid liberated. The number of equivalents of acid from one mole of pinitol was 2·92 (1·8 hours); 3·71 (24 hours); 3·74 (48 hours); 3·97 (8 days); and 4·16 (after 20 minutes on boiling water-bath). For *meso*inositol, 5·10 (2 hours); 5·18 (19 hours); 5·13 (25 hours); 5·03 (43 hours); 5·04 (70 hours); 5·01 (144 hours). These titrations were with 0·01N-barium hydroxide (methyl-red).

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133. *The Determination of Vapour Pressures of the Order of 1 mm. of Mercury by a Modification of Smith and Menzies's Method. The Vapour Pressure of Dimethylnitramine.*

By R. S. Bradley, S. Cotson, and E. G. Cox.

A modification is described of the method devised by Smith and Menzies (*J. Amer. Chem. Soc.*, 1910, **32**, 907) for measuring vapour pressures of the order of 1 mm.

The substance was contained in a small bulb attached to a capillary tube (diameter about 2 mm.) and placed in a holder in the apparatus as shown in Fig. 1. The U-tube contained previously degassed medicinal paraffin, the surface of which was initially just below the tip of the capillary tube. The system was evacuated with the tap *A* open; *A* was then closed and the height of paraffin oil in the left-hand limb raised by letting in small amounts of air through *B* and *C* so that the rate of evolution of bubbles of vapour from the capillary tip was thus progressively reduced. It was found in practice that because of very slow dissolution of the vapour in the paraffin, no equilibrium position at which bubbles were just about to be

Fig. 1.

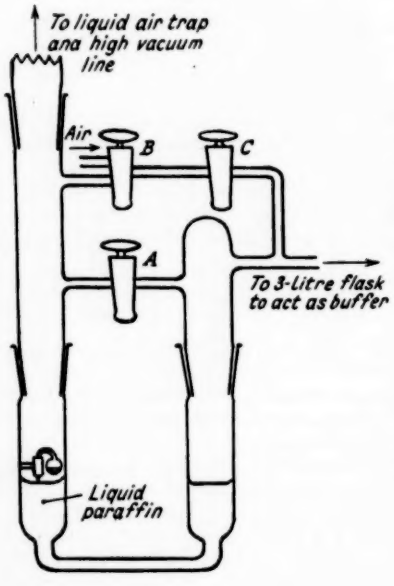
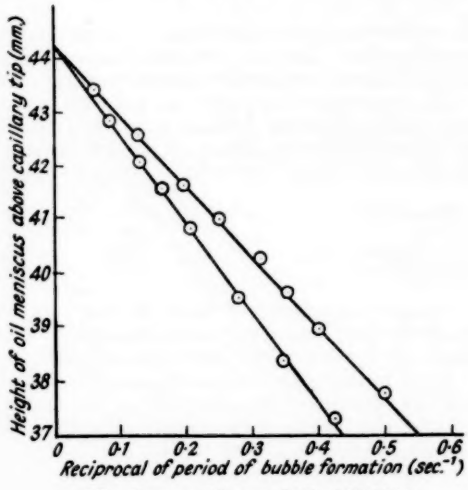


Fig. 2.



(*For 2 runs with same bulb at* 49·04°.)

released could be obtained. The same phenomenon was observed when the liquid paraffin was replaced by other non-volatile liquids *e.g.*, dibutyl phthalate and phosphoric acid.

A kinetic method was therefore adopted and the rate of bubble formation at various pressures of oil determined. In most cases the plot of oil pressure against the reciprocal of the period of bubble formation gave a straight line over a range of several mm. of oil just below the theoretical equilibrium pressure (Fig. 2). By extrapolation to the point where the reciprocal of the time was zero, the equilibrium pressure of oil was then obtained. This value was found to be reproducible (to within 1%).

In order to obtain the vapour pressure of the substance, it was then only necessary to correct the equilibrium pressure for the surface tension effect in the capillary. The pressure above the surface of the liquid paraffin on the high-vacuum side was so small as to be negligible.

This correction was determined in a subsidiary experiment. A length of capillary tubing which had been broken off the piece used to make the bulb in the first case was suspended vertically in a boiling-tube. The lower end had exactly the same internal radius as the end of

the tube attached to the bulb, since the capillary was broken off at this point to make the bulb. Liquid paraffin was poured into the boiling-tube until the height of the oil surface above the tip was the same as in the kinetic experiment. The upper end of the capillary tube was then attached to a dibutyl phthalate manometer and a mercury dropper which forced air through the system, causing bubbles to appear slowly and regularly at the tip of the tube. The pressure registered on the manometer then gave the combined pressure due to depth of oil and surface tension effect, *i.e.*, the absolute vapour pressure. It was assumed that the difference between the surface tension for the oil–vapour and the oil–air interfaces was negligible. Experiment showed that there was no appreciable reduction in the surface tension of the oil due to dissolution of the vapour.

The method gave values for the vapour pressure of iodine in reasonable agreement (to within $\pm 1{\cdot}5\%$) with those previously published (Gillespie and Frazer, *ibid.*, 1936, **58**, 2260).

The vapour pressure of dimethylnitramine was determined over a range of temperatures, with the following results :

T (c.)	41·70°	43·34°	45·24°	47·35°	49·04°	50·72°
P (mm. of Hg)	1·60	1·85	2·15	2·60	2·95	3·37

The plot of $\log_{10} P$ against $1/T$ gave a straight line reproduced by

$$\log_{10} P \text{ (mm. of Hg)} = 11{\cdot}80 - 3650/T$$

The latent heat of sublimation is 16,700 cals./mole.

An attempt was made to confirm the above figures by means of the Knudsen effusion method, but it was found difficult to obtain reproducible results. This was attributed to stray particles of solid partly blocking the hole in the effusion vessel; this hole was necessarily very fine, to fulfil the mean-free-path requirements and to avoid errors due to self-cooling.

We acknowledge gratefully the award of a Monsanto Chemicals research grant to one of us (S. C.).

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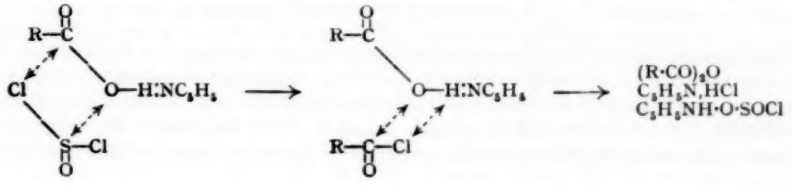
134. *The Function of Pyridine in the Carboxylic Acid–Thionyl Chloride System.*

By W. GERRARD and A. M. THRUSH.

DURING a systematic investigation of the carboxylic acid–thionyl chloride system it was observed that addition of thionyl chloride (0·5 mol.) to an ethereal solution of acetic acid (1 mol.) and pyridine (1 mol.) gave an immediate precipitation of what appeared to be an equimolecular mixture of pyridine hydrochloride and $C_5H_5NH^+ \ ^-O{\cdot}SOCl$, and from the ethereal solution acetic anhydride was obtained in 97% yield. In a similar way high yields of *iso*butyric, *iso*valeric, and *n*-heptanoic anhydrides were obtained.

The method for the preparation of heptanoic anhydride described in *Org. Synth.*, 1946, **26**, 1, entails addition of heptanoyl chloride to pyridine in benzene to effect the formation of a pyridinium complex, to which is added the heptanoic acid. We do not invoke the formation of a complex between pyridine and acyl chloride to explain *our* result, but instead postulate a mechanism entailing the four-centre broadside approach of the reacting molecules :



Discussing the use of pyridine to facilitate formation of acyl chloride, McMaster and Ahmann (*J. Amer. Chem. Soc.*, 1928, **50**, 145) refer to it as an inert solvent in one place, and as a catalyst in another; but there is now no doubt that it plays an essential part in the reaction sequences with regard to the acids of the type referred to above. Nevertheless, in describing these systems it is necessary to pay due attention to the degree of reactivity of the acyl carbon and chlorine atoms. Whereas McMaster and Ahmann were not able to prepare trichloroacetyl chloride by means of thionyl chloride alone, Carré and Libermann (*Compt. rend.*, 1934, **199**, 1422; cf. Mills and Human, *Nature*, 1946, **158**, 887) obtained this in 90% yield when pyridine was used. It is noteworthy that preliminary experiments now indicate that addition of thionyl chloride to an ethereal solution of trichloroacetic acid and pyridine (present largely as the precipitated salt) appears to involve only the first reaction to the acyl chloride, and not the second one to the anhydride. This may conceivably be due to a considerable increase in velocity of the first reaction owing to a decreased electron density on the acyl carbon atom and an increase on the acyl oxygen atom, $CCl_3 \cdot CO \cdot O^-$, and a decrease in velocity of the second reaction due to reduction in the reactivity of the acyl chlorine atom in acyl chloride.

Experimental.—Dry ether and pyridine, and redistilled thionyl chloride and acids were used. Dropwise addition of thionyl chloride (5·9 g., 0·5 mol.) in ether (5 c.c.) to an ethereal (30 c.c.) solution of acetic acid (6·0 g., 1 mol.) and pyridine (7·9 g., 1 mol.) at −10° afforded immediately a white precipitate, which was separated, washed rapidly with ether, and dissolved in water. The aqueous solution contained C_5H_5N, 0·096 g.-mol. (Calc.: 0·10 g.-mol.); Cl^-, 0·096 g.-ion; and SO_2, 0·042 g.-mol. (Calc: 0·05 g.-mol.). From the ethereal solution acetic anhydride (5·0 g., 97%), b.p. 138° (Found: equiv., 51·7. Calc.: equiv., 51·0), was obtained. As the precipitate tends to lose sulphur dioxide even on the short exposure during filtration, this operation was then performed in a flask fitted with a side arm containing a sintered-glass partition. The aqueous solution of the precipitate then contained C_5H_5N, 0·0975 g.-mol.; Cl^-, 0·0965 g.-ion; SO_2, 0·050 g.-mol. When the reaction was carried out at −80°, the aqueous solution of the precipitate contained: C_5H_5N, 0·099 g.-mol.; Cl^-, 0·097 g.-ion; SO_2, 0·050 g.-mol. These data indicate an equimolecular mixture of pyridine hydrochloride and the salt $C_5H_5NH \cdot O \cdot SOCl$.

By the same procedure and from the same weights of thionyl chloride and pyridine, *iso*-butyric anhydride (7·8 g., 98%), b.p. 180—183°, d_4^{20} 0·9535, n_D^{19} 1·4061, was obtained from the acid(8·8 g.). The aqueous solution of the precipitate (open filtration) contained: C_5H_5N, 0·091 g.-mol.; Cl^-, 0·097 g.-ion; SO_2 0·04 g.-mol.

Similarly from *iso*valeric acid (10·2 g.) the anhydride (9·2 g., 99%), b.p. 100—103°/15 mm., d_4^{27} 0·9260, n_D^{21} 1·4150 (Found: equiv., 93·9. Calc.: equiv., 93·0) was obtained. The aqueous solution of the precipitate contained: C_5H_5N, 0·094 g.-mol.; Cl^-, 0·097 g.-ion; SO_2, 0·04 g.-mol.

n-Heptanoic acid (13·0 g.) afforded the anhydride (11·75 g., 97%), b.p. 102—109°/0·5 mm., 258°/754 mm., d_4^{15} 0·9215, redistilled (7·4 g. from 7·6 g.), b.p. 104—108°/0·4 mm., n_D^{21} 1·4320 (Found: equiv., 121·7. Calc.: equiv., 121·0).

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135. *A Convenient Reagent for the Preparation of Thioamides, and the Thiohydrolysis of* S-*Alkyl*isothiourea *Derivatives.*

By A. E. S. FAIRFULL, J. L. LOWE, and D. A. PEAK.

THE preparation of thioamides from cyanides is usually accomplished by heating the cyanide under pressure with an alcoholic solution of either an alkali-metal hydrogen sulphide or an ammonium (or substituted ammonium) hydrogen sulphide (*e.g.*, Gabriel and Heymann, *Ber.*, 1890, **23**, 158; Kindler and Burghard, *Annalen*, 1923, **431**, 201). Olin and Johnson (*Rec. Trav. chim.*, 1931, **50**, 72) converted a number of acylated cyanohydrins into the corre-

sponding thioamides by the addition of hydrogen sulphide at room temperature in alcohol in the presence of triethanolamine but they did not extend the reaction to other cyanides. Renfrew (*J. Amer. Pharm. Assoc.*, 1951, **40**, 467) has recently applied the method to the preparation of 7-methylthiocinchoninamide but the addition took many hours.

We have found that the addition of hydrogen sulphide to aromatic cyanides takes place with remarkable ease in pyridine solution in the presence of a strong base such as triethylamine. Reaction is complete at room temperature in 2—4 hours and the thioamide is obtained, usually in good yield and often in a state of high purity, by pouring the reaction mixture into water. The reaction is equally applicable to other types of cyanides such as cyanamides, aminomethyl cyanides, and azomethyl cyanides. With benzyl cyanide the addition is sluggish and takes about 20 hours. With aliphatic cyanides, such as methyl or octyl cyanides, the addition is so slow that the method offers no advantage over the conventional pressure methods.

Triethylamine was used throughout this work in molar proportion. Presumably other strong bases would be equally effective and catalytic quantities might suffice, but these points have not been investigated. The presence of the strong base is essential since addition occurs at a negligible rate in its absence. Pyridine acts as an excellent solvent for most cyanides but its rôle is not purely passive since it also promotes addition. Thus, the rate of addition of hydrogen sulphide to *p*-methoxyphenyl cyanide is many times greater in pyridine–triethylamine than in chloroform–triethylamine. In the one case tried, benzyl cyanide, the rate of addition was also much greater than with the ethanol–triethanolamine mixture used by Olin and Johnson (*loc. cit.*). These authors mentioned the use of pyridine but were deterred from adopting it because of its desulphurising action on thioamides. This reason is hardly valid since the desulphurising action appears to be appreciable only at high temperatures for long periods (Raffo and Rossi, *Gazzetta*, 1914, **44**, 104; 1915, **45**, 28).

The pyridine need not be specially purified, commercial pyridine proving quite satisfactory. Anhydrous conditions facilitate the addition. Thus, the use of undried hydrogen sulphide reduces the yield of thiobenzamide from phenyl cyanide. This is not due to the simultaneous formation of benzamide since the pyridine–triethylamine mixture does not catalyse the addition of water to phenyl cyanide under comparable conditions.

The reagent is equally effective for the thiohydrolysis of *S*-alkyl*iso*thiourea derivatives to the corresponding thiourea derivatives. This has hitherto been accomplished in boiling alcoholic sodium or potassium hydrogen sulphide (Olin and Dains, *J. Amer. Chem. Soc.*, 1930, **52**, 3326; Underwood and Dains, *Kansas Univ. Sci. Bull.*, 1937, **24**, 5). In pyridine–triethylamine the reaction proceeds rapidly at room temperature. By this means representatives of several types of compounds, including *S*-alkyl-*iso*thioureas, -*iso*dithiobiurets, and -*iso*thiosemicarbazones, have been successfully thiohydrolysed. With *N*-*p*-chlorophenyl-*N'*-cyano-*S*-ethyl*iso*thiourea simultaneous thiohydrolysis and addition of hydrogen sulphide occur with the production of 1-*p*-chlorophenyldithiobiuret.

Thiohydrolysis also proceeds in the absence of triethylamine but at a considerably reduced rate.

Experimental.—Preparation of thioamides. The cyanide is dissolved in at least an equal weight of pyridine (more if the cyanide is of low solubility) and triethylamine (1 mol.) is added. Dry hydrogen sulphide is passed through the solution in a steady stream for 2—4 hours. The mixture is then poured into water, and the thioamide collected by filtration and, if necessary, crystallised from a suitable solvent.

The following thioamides were prepared in this manner. The yields recorded are those of pure product, or of unrecrystallised product of stated m. p. where this was close to that of the pure compound, as was frequently the case. No detailed investigation was made in any preparation and the yields are not necessarily optimum, especially as regards the recoveries on recrystallisation of the crude products.

Thiobenzamide (94%), m. p. 116° (Bernthsen, *Ber.*, 1877, **10**, 1241, records m. p. 115—116°); *p*-methoxythiobenzamide (90%), m. p. 149° after recrystallisation from xylene (Rehländer, *Ber.*, 1894, **27**, 2159, records m. p. 148—149°); *p*-chlorothiobenzamide (48·5%), needles or prisms (from benzene), m. p. 129—130° (Kindler, *Annalen*, 1926, **450**, 13, records m. p. 124°);

o-*chlorothiobenzamide* (100%; m. p. 57°), needles, m. p. 62·5—63°, from benzene–light petroleum (Found: C, 49·35; H, 3·5. C_7H_6NClS requires C, 49·0; H, 3·5%); *p*-aminothiobenzamide 81·5%; m. p. 168—170°), pale-yellow needles or plates, m. p. 180°, from water (Bogert, *J. Amer. Chem. Soc.*, 1903, **25**, 483, and Engler, *Annalen*, 1869, **149**, 297, record m. p.s 172° and 170° respectively); *p*-acetamidothiobenzamide (80%), pale yellow needles, m. p. 216°, from aqueous ethanol (MacCorquodale and Johnson, *Rec. Trav. chim.*, 1932, **51**, 483, record m. p. 215°); p-*ethylsulphonylthiobenzamide* (70%), pale yellow needles, m. p. 181—182°, from ethanol (Found: N, 6·05. $C_9H_{11}O_2NS_2$ requires N, 6·1%); 3 : 4-dimethoxythiobenzamide (70%), pale yellow needles, m. p. 184—185°, from ethanol (Hinegardner and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 4141, record m. p. 183°); dithioterephthalamide (60·5%; m. p. 260°) (Luckenbach, *Ber.*, 1884, **17**, 1430, records m. p. 263°); phenyl(thioacetamide) (95%; m. p. 95°), m. p. 97° after one recrystallisation from benzene–light petroleum (Bernthsen, *Annalen*, 1876, **184**, 292, records m. p. 97·5—98°); thionicotinamide (86%; m. p. *ca.* 175—183°), m. p. 183° (decomp.) after recrystallisation from water (Karrer and Schukri, *Helv. Chim. Acta*, 1945, **28**, 820, record m. p. 180—181°); thiopicolinamide (65·5%; m. p. 136°) (*idem*, *loc. cit.*, record m. p. 137°); *p*-methoxyphenylthiourea (90%; m. p. 204—205°), m. p. 210—211° after two recrystallisations from ethanol (Dyson and George, *J.*, 1924, **125**, 1708, record m. p. 210—211°); anilino(thioacetamide) * (83%), m. p. 165—166° (slight decomp.) after recrystallisation from ethanol [Paradies, *Ber.*, 1903, **36**, 4302, and Johnson and Burnham, *J. Amer. Chem. Soc.*, 1912, **47**, 239, record m. p.s 165° and 166° (decomp.) respectively]; (*N*-benzylanilino)thioacetamide * (83%), m. p. 176° after recrystallisation from ethanol (Turner and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 3081, record m. p. 176—178°); *phenylazo*(*thioacetamide*) (75%), yellow prisms (from methanol), m. p. 185—186° (Found: C, 53·5; H, 4·6. $C_8H_9N_3S$ requires C, 53·6; H, 5·0%).

Thiohydrolyses. The *S*-alkyl*iso*thiourea derivative is dissolved or suspended in pyridine (2—8 parts by weight) and triethylamine (1·1 mols.) added. An additional 1 mol. of triethylamine is added if the *iso*thiourea is in the form of a salt. Dry hydrogen sulphide is passed through the solution at room temperature for 4 hours and the reaction mixture poured into water. The solid is collected and washed with a little dilute acetic acid.

In this way *S*-ethyl-*N*-phenyl*iso*thiourea hydriodide gave *N*-phenylthiourea (60%), m. p. 148—151°, or 149—151° when mixed with authentic *N*-phenylthiourea (m. p. 151—152°); *S*-methyl*iso*thiocarbanilide gave thiocarbanilide (92%), m. p. 150—152°, or 151—152° when mixed with authentic thiocarbanilide (m. p. 153—154°); 2 : 4-dimethyl-1 : 5-diphenyl-2 : 4-di*iso*dithiobiuret (Johnson and Elmer, *Amer. Chem. J.*, 1903, **30**, 167) gave 1 : 5-diphenyldithiobiuret (75%), felted needles (from ethanol), m. p. 148—149° not depressed by a sample (m. p. 147—148°) prepared by the method of Olin and Dains (*loc. cit.*); benzaldehyde *S*-ethyl-*iso*thiosemicarbazone hydrobromide gave benzaldehyde thiosemicarbazone (44%), m. p. and mixed m. p. 158—160° after purification of the initial crude product (m. p. 145—150°) by dissolution in aqueous sodium hydroxide, filtration, and precipitation with acetic acid; and *N*-*p*-chlorophenyl-*N'*-cyano-*S*-methyl*iso*thiourea (Crowther, Curd, Richardson, and Rose, *J.*, 1948, 1639) gave 1-*p*-chlorophenyldithiobiuret (75%), felted needles (from ethanol), m. p. 176—178° not depressed by a sample of 1-*p*-chlorophenyldithiobiuret, m. p. 179—180° (Found: N, 16·9. Calc. for $C_8H_8N_3ClS_2$: N, 17·1%), prepared by a modification of the method of Fernandos and Ganapathi (*Proc. Indian Acad. Sci.*, 1948, **37**, 570) who, however, record m. p. 163—164°.

When triethylamine was omitted, the yield of thiocarbanilide from *S*-methyl*iso*thiocarbanilide was only 61% after 4 hours under comparable conditions to the above.

The authors thank Dr. W. F. Short for his interest in this work.

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* Preparations by Dr. N. W. Bristow.

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